Liquid Dosage Forms to Treat Cancer

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Application Serial Number 62/517,736, filed June 9, 2017, and U.S. Application Serial Number 62/520,768, filed June 16, 2017. The entire contents of the aforementioned applications are incorporated herein by reference.

Field of Invention

[0002] This invention relates to a liquid pharmaceutical formulation comprising an L-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Background of the Invention

[0003] Multi-targeted tyrosine kinase inhibitors (TKIs) chemotherapeutics have been instrumental in the recent advancements of anticancer treatment over the past several years. Tyrosine kinase inhibitor therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types including renal cell carcinoma (RCC), urothelial carcinoma (UC), melanoma, non-small-cell lung cancer (NSCLC), and others. The success of this therapy type as a single agent has naturally led to interest in evaluating novel formulations that provide enhanced pharmacokinetics (PK) and pharmacodynamics (PD) of TKIs when used in combination with checkpoint inhibitors in search of further, possibly synergistic, anticancer clinical effects.

[0004] Medicaments, such as chemotherapeutic drugs that are administered orally, are dispensed to the patient in several dosage forms, including liquid forms such as solutions, syrups, emulsions, and suspensions, and more commonly, in solid forms such as capsules, caplets, and tablets. Children, older persons, and many other persons (including disabled or incapacitated patients) often have trouble swallowing tablets or capsules. In these situations, it is desirable to provide the drug either in a chewable solid form or a liquid form. Pharmaceutically active agents administered in solid dosage form are usually intended to be swallowed whole. In some cases, the unpleasant taste of the medicament in solid form is generally not of concern when formulating oral solid dosage forms, because the pharmaceutical's taste can be easily masked with an exterior coating.

[0005] However, despite the convenience of formulating medicaments in oral solid forms, for pediatric and geriatric patients, a liquid oral dosage form is preferred over a

chewable dosage form. A liquid dosage form is especially preferred for pediatric and geriatric patients because of the ease with which it may be swallowed. Additionally, patients may be more inclined to comply with their medication instruction if the dosages are easier to ingest, particularly for products administered in large doses, requiring several tablets at a time.

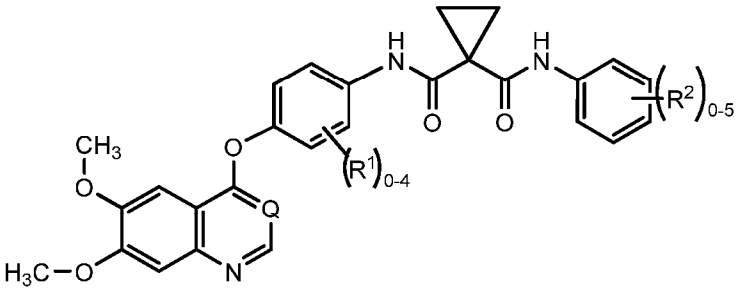
[0006] Some liquid pharmaceutical compositions formulated for use by pediatric or geriatric patients are prepared by grinding a tablet dosage form into a powder and mixing the powder with a diluent. Such a formulation may cause some of the drug to remain undissolved, thereby affecting the therapeutic dose of drug in the composition. In addition, the powder exposes the unpleasant tasting pharmaceutically active agent, which may result in a lack of compliance due to the unacceptable taste. It is readily understood that such compositions are impractical and may result in underdosing or poor compliance.

Summary of the Invention

[0007] The problem underlying the present invention is to provide a liquid dosage form containing a compound of Formula I, or a pharmaceutically acceptable salt thereof, which does not show the above-described disadvantages of the known dosage forms. In particular, the pharmaceutical formulation should be stable over a long time period, as well as physiologically acceptable and pleasing for pediatric and geriatric patients. In some embodiments, the liquid formulations of the present invention find utility in the treatment of cancer, for example, for the treatment of a solid tumor in a patient in need thereof.

[0008] In some embodiments, the solid tumor is a locally advanced or a metastatic solid tumor.

[0009] In some embodiments, the present invention is directed to a liquid pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

or a liquid pharmaceutical composition comprising the compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, wherein:

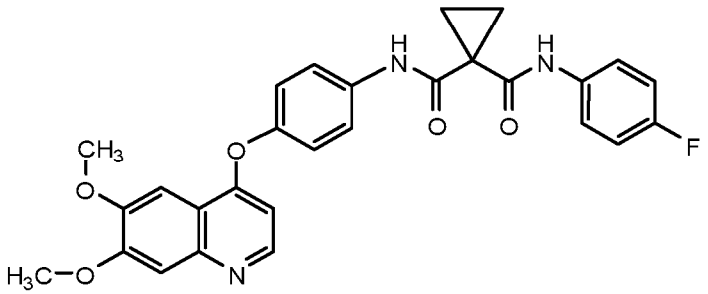
R^1 is halo;

R^2 is halo; and

Q is CH or N.

[0010] In various embodiments, a single dose of the liquid pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, for example, compound 1, or a pharmaceutically acceptable salt thereof, provides an interpatient or intrapatient exposure variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10%. In various embodiments, the exposure is represented by a noncompartmental PK parameter selected from the group consisting of: AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, C_{max}, t_{max}, k_{el}, and $t_{1/2}$. In some embodiments, the liquid formulation of the present invention when dosed as a single dose provides an AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, or a C_{max} interpatient or intrapatient variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10%. In some embodiments, the liquid formulation of the present invention when dosed as a single dose provides an AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, or C_{max} interpatient or intrapatient variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10% relative to a tablet formulation containing a compound of formula I, or a pharmaceutically acceptable salt thereof, for example, compound 1, or a pharmaceutically acceptable salt thereof. In the above related embodiments, the single dose can include a single dose of about: 200 mg, 190 mg, 180 mg, 170 mg, 160 mg, 150 mg, 140 mg, 130 mg, 120 mg, 110 mg, 100 mg, 90 mg, 80 mg, 70 mg, 60 mg, 50 mg, 40 mg, 30 mg, 20 mg, or 10 mg of a compound of formula I, or compound 1 which can be the (L)-malate salt (also referred to herein as the S-malate salt; S-malate salt and (L)-malate salt are used interchangeably herein) or the (D)-malate salt (also referred to as the R-malate salt; R-malate salt and (D)-malate salt are used interchangeably herein). In various embodiments, the above referenced single doses comprises cabozantinib. Cabozantinib is also referred to as XL184, and XL184 and cabozantinib are used interchangeably herein.

[0011] Another aspect is directed to a method of treating a locally advanced or metastatic solid tumor, comprising administering to a patient in need of such treatment a liquid pharmaceutical composition comprising compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof or a liquid pharmaceutical composition comprising compound 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0012] In some aspects, the locally advanced or a metastatic solid tumor may be advanced UC (urothelial carcinoma) or RCC (renal cell carcinoma).

[0013] In another aspect, the invention comprises a liquid pharmaceutical dosage form comprising a compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, such that each dose of the liquid pharmaceutical composition comprising compound 1, or a pharmaceutically acceptable salt thereof provides the patient an interpatient or intrapatient exposure (for example, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, C_{max}, or t_{max}) variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10% relative to a tablet formulation containing the same amount of compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof.

Brief Description Of The Figures

[0014] FIG. 1 depicts a line graph of the mean (±SD) cumulative excretion of urine and feces total radioactivity following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects (N=8).

[0015] FIG. 2 depicts a line graph of the mean (±SD) plasma total radioactivity in plasma and whole blood and XL184 concentration (by LC/MS/MS method) vs. time 0-648 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - linear axes (N=8)

[0016] FIG. 3 depicts a line graph of the mean (±SD) plasma total radioactivity in plasma and whole blood and XL184 concentration (by LC/MS/MS method) vs. time 0-120 hours

following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - linear axes (N=8)

[0017] FIG. 4 depicts a line graph of the mean (±SD) plasma total radioactivity in plasma and whole blood and XL184 concentration (by LC/MS/MS method) vs. time 0-648 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - semilogarithmic axes (N=8).

[0018] FIG. 5 depicts a line graph of the mean (±SD) plasma total radioactivity in plasma and whole blood and XL184 concentration (by LC/MS/MS method) vs. time 0-120 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - semilogarithmic axes (N=8).

[0019] FIG. 6 depicts a line graph of the mean (±SD) percentage of 14C radioactivity associated with erythrocytes in whole blood over time graph following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects (N=8).

[0020] FIG. 7 depicts a line graph of the mean (±SD) plasma concentrations of XL184 and metabolites XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by LC/MS/MS method vs. time 0-648 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - linear axes (N=8).

[0021] FIG. 8 depicts a line graph of the mean (±SD) plasma concentrations of XL184 and metabolites XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by LC/MS/MS method vs. time 0-120 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - linear axes (N=8).

[0022] FIG. 9 depicts a line graph of the mean (±SD) plasma concentrations of XL184 and metabolites, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by LC/MS/MS method vs. time 0-648 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - semilogarithmic axes (N=8).

[0023] FIG. 10 depicts a line graph of the mean (±SD) plasma concentrations of XL184 and metabolites, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by LC/MS/MS method vs. time 0-120 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects - semilogarithmic axes (N=8).

[0024] FIG. 11 depicts a line graph of the mean (±SD) plasma concentrations of demethyl half-dimer sulfate, P5, P7, XL-184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by radio-quantitation method vs. time 0-336 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects - linear axes.

[0025] FIG. 12 depicts a line graph of the mean (±SD) plasma concentrations of demethyl half-dimer sulfate, P5, P7, XL-184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by radio-quantitation method vs. time 0-80 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects - linear axes.

[0026] FIG. 13 depicts a line graph of the mean (±SD) plasma concentrations of demethyl half-dimer sulfate, P5, P7, XL-184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by radio-quantitation method vs. time 0-336 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects - semilogarithmic axes.

[0027] FIG. 14 depicts a line graph of the mean (±SD) plasma concentrations of demethyl half-dimer sulfate, P5, P7, XL-184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate measured by radio-quantitation method vs. time 0-80 hours following a single 175 mg oral administration of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects - semilogarithmic axes.

[0028] FIG. 15 depicts proposed major biotransformation products of XL184 (cabozantinib).

Definitions

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic-pyruvate transaminase)
Anti-HAV	Hepatitis A total antibody
Anti-HBc	Hepatitis B core antigen antibody
Anti-HBs	Hepatitis B surface antigen antibody
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}24}$	Area under the concentration-time curve from time zero to time 24 hours
$AUC_{0\text{-}72}$	Area under the concentration-time curve from time zero to time 72 hours
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero to time of the last measurable concentration

BMI	Body mass index
BUN	Blood urea nitrogen
°C	Degrees Celsius
Chem	Chemistry
C_{max}	Maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
%CV	Percentage coefficient of variation
CYP	Cytochrome P450
% $Dose_{(feces)}$	Percentage of dose recovered in feces over the collection interval
% $Dose_{(urine)}$	Percentage of dose recovered in urine over the collection interval
ECG	Electrocardiogram
eCRF	Electronic case report form
ETR	Percentage of ^{14}C radioactivity associated with erythrocytes in whole blood
°F	Degrees Fahrenheit
g	Gram
GI	Gastrointestinal
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibodies
Hem	Hematology
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IGm	Immunoglobulin M
INN	International Nonproprietary Name
LLOQ	Lower limit of quantification
IRB	Institutional Review Board
k_{el}	Apparent terminal elimination rate constant
kg	Kilogram
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
m	Meter
MBq	Megabecquerel
MedDRA®	Medical Dictionary for Regulatory Activities
MET	Hepatocyte growth factor receptor protein
mg	Milligram
µCi	Microcurie
mL	Milliliter
mmHg	Micrometers of mercury
msec	millisecond
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute

NE	Not estimated
ng	Nanogram
ngEq	An equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity
NR	Not reportable
p-FA	Para-fluoroaniline
PK	Pharmacokinetic
PO	Oral
QTc	Corrected QT interval
RBC	Red blood cell
RET	Rearranged during transfection
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum concentration
$t_{½}$	Apparent terminal elimination half-life calculated as $\ln(2)/k_{el}$
UPCr	Urine Protein/Creatinine ratio
US	United States of America
USAN	United States Adopted Name
VEGFR2	Vascular endothelial growth factor receptor 2
WBC	White blood cell
WHO	World Health Organization
XL184	The product number used by Exelixis for development of the compound with the USAN/INN designation of cabozantinib

Detailed Description

[0029] As indicated above, the invention is directed to a method of treating a locally advanced or a metastatic solid tumor, comprising administering a liquid formulation of a compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof.

[0030] Compound 1 is known by its chemical name N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and by the name cabozantinib (also referred to as XL184). COMETRIQ™ (Cabozantanib S-Malate oral capsules) has been approved by the Food and Drug Administration (FDA) in the United States on November 29, 2012, for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). CABOMETYX™ (Cabozantanib S-Malate oral tablets) has been approved by the Food and Drug Administration (FDA) in the United States on April 25, 2016, for the treatment of advanced renal cell carcinoma (RCC) in patients who have

received prior antiangiogenic therapy. Cabozantinib is formulated as the L-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. WO 2005/030140, the entire contents of which is incorporated herein by reference, discloses compound, describes how it is made (Example 48), and discloses the therapeutic activity of this compound to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289). Example 48 begins at paragraph [0353] in WO 2005/030140. Information for compound 1 is available from the FDA at http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208692 (last visited December 19, 2016) and is incorporated herein by reference in its entirety.

[0031] In various embodiments, the present invention provides a pharmaceutical composition formulated for oral administration in liquid form. When compared to solid forms, for example, a formulation in tablet, capsule, sachet, or powdered form, the liquid pharmaceutical compositions of the present invention comprising a compound of formula I or compound 1, which can be the (L)-malate salt or the (D)-malate salt, provides a significantly smaller interpatient or intrapatient variability in exposure. For example, as published in Nguyen, L. et al., "Pharmacokinetics of cabozantinib tablet and capsule formulations in healthy adults," (2016), *Anti-Cancer Drugs* 2016, 27:669–678, (the disclosure of which is incorporated herein by reference in its entirety), the values of C_{max}, AUC_{0-t}, and AUC_{0-inf} plasma pharmacokinetic parameters were highly variable among study participants, ranging from (i.e. %CV about 48–72%, 42–56%, and 38–41% for the 20, 40, and 60 mg (free base equivalent, FBE) cabozantinib tablet strength treatments, respectively). Table 1 (reproduced from the Nguyen, L. et al., reference cited herein) summarizes the plasma PK parameters found when healthy patients were dosed with a single dose of 140 mg (free base equivalent, FBE) of cabozantinib or the malate salt of compound 1. The values of C_{max}, AUC_{0-t}, and AUC_{0-inf} plasma pharmacokinetic parameters were highly variable among study participants (i.e. %CV about 54%, 44%, 46% and 43%, 37%, and 39% for the 140 mg (free base equivalent, FBE) cabozantinib tablet and capsule dose treatments, respectively).

[0032] **Table 1. Summary of cabozantinib plasma pharmacokinetic parameters from healthy individuals administered a single oral dose of tablet or capsule formulations containing 140 mg of cabozantinib (free base equivalent, FBE).**

Pharmacokinetic parameter	Tablet treatment (mean ± CV%)[a]	Capsule treatment (mean ± CV%)[b]

C_{max} (ng/ml)	702 ± 54	554 ± 43
t_{max} (h)[c]	3.49 (1.99, 24.00)	4.00 (2.00, 5.04)
AUC_{0-t} (ng × h/ml)	61 900 ± 44	54 900 ± 37
AUC_{0-inf} (ng × h/ml)	65 800 ± 46	58 300 ± 39
$t_{1/2}$ (h)	115 ± 31	112 ± 26
CL/F (l/h)	2.61 ± 49	2.69 ± 32
VZ/F (l)	424 ± 58	426 ± 37

AUC, area under the plasma concentration-time curve; CL/F, oral clearance; CV, coefficient of variation.

[a]Treatment A (test): 140 mg dose (2 × 20 + 1 × 100 mg) of XL184 (cabozantinib) tablet formulation; (n = 72).

[b]Treatment B (reference): 140 mg dose (3 × 20 + 1 × 80 mg) of XL184 (cabozantinib) capsule formulation; (n = 72).

[c]Median (minimum, maximum) are presented.

[0033] In these and other embodiments, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered as a liquid pharmaceutical composition, wherein the liquid pharmaceutical composition additionally comprises a pharmaceutically acceptable carrier, excipient, or diluent. In a specific embodiment, the compound of formula I is compound 1, or a pharmaceutically acceptable salt thereof.

[0034] The compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof as described herein, includes both the recited compounds as well as individual isomers and mixtures of isomers. In each instance, the compound of formula I includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

[0035] In other embodiments, the compound of formula I or compound 1 can be the (L)-malate salt (also referred to herein as the S-malate salt), or the (D)-malate salt (also referred to as the R-malate salt). The malate salt of the compound of formula I and of compound 1 is disclosed in PCT/US2010/021194 and U.S. Patent Application Serial No. 61/325095, the entire contents of each of which are incorporated herein by reference.

[0036] In other embodiments, the compound of formula I can be malate salt.

[0037] In other embodiments, the compound of formula I can be the (D)-malate salt.

[0038] In other embodiments, the compound of formula I can be the (L)-malate salt.

[0039] In other embodiments, compound 1 can be the malate salt.

[0040] In other embodiments, compound 1 can be (D)-malate salt.

[0041] In other embodiments, compound 1 can be the (L)-malate salt.

[0042] In another embodiment, the malate salt is in the crystalline N-1 form of the (L) malate salt and/or the (D) malate salt of the compound 1 as disclosed in U.S. Patent Application Serial No. 61/325095. In another embodiment, the malate salt is the crystalline N-2 form of the (L) malate salt and/or the (D) malate salt of the compound 1 as disclosed in U.S. Patent Application Serial No. 61/325095. In yet another embodiment, the malate salt is a mixture of the N-1 and N-2 forms of the (L) malate salt and/or the (D) malate salt of the compound 1 as disclosed in U.S. Patent Application Serial No. 61/325095. See also WO 2008/083319 for the properties of crystalline enantiomers, including the N-2 crystalline forms of the (L)-malate salt (also referred to as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt), and/or the N-1 crystalline forms of the (L)-malate salt (also referred to as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt) of compound 1. Methods of making and characterizing such forms are fully described in PCT/US10/21194, which is incorporated herein by reference in its entirety.

[0043] In one embodiment, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered once daily. In a further embodiment, a compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered with fasting (i.e., without eating) for approximately two hours before and 1 hour after administration.

[0044] In another embodiment, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered orally once daily as a liquid formulation.

[0045] In another embodiment, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered orally as its free base or malate salt as a liquid formulation.

[0046] In various embodiments, a single dose of the liquid pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, for example, compound 1, or a pharmaceutically acceptable salt thereof, provides an interpatient or intrapatient exposure variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10%. In various embodiments, the exposure is represented by a noncompartmental PK parameter selected from the group consisting of: AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, C_{max}, t_{max}, k_{el}, and $t_{1/2}$. In some embodiments, the liquid formulation of the present invention when dosed as a single dose provides an AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, or a C_{max} interpatient or intrapatient

variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10%. In some embodiments, the liquid formulation of the present invention when dosed as a single dose provides an AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, AUC_{0-inf}, or C_{max} interpatient or intrapatient variability of less than 30%, or less than 25%, or less than 20%, or less than 19%, or less than 18%, or less than 17%, or less than 16%, or less than 15%, or less than 14%, or less than 13%, or less than 12%, or less than 11%, or less than 10% relative to a tablet formulation containing a compound of formula I, or a pharmaceutically acceptable salt thereof, for example, compound 1, or a pharmaceutically acceptable salt thereof.

[0047] In the above related embodiments, the single dose can include a single dose of about: 200 mg, 190 mg, 180 mg, 170 mg, 160 mg, 150 mg, 140 mg, 130 mg, 120 mg, 110 mg, 100 mg, 90 mg, 80 mg, 70 mg, 60 mg, 50 mg, 40 mg, 30 mg, 20 mg, or 10 mg of a compound of formula I or compound 1, which can be the (L)-malate salt (also referred to herein as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt). In various embodiments, the above referenced single doses comprises cabozantinib.

[0048] The amounts of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, that are administered will vary. In one embodiment, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered in an amount of from about 1 mg to about 200 mg, or from about 5 mg to about 175 mg, or from about 10 mg to about 100 mg, for example, 190 mg, 180 mg, 170 mg, 160 mg, 150 mg, 140, mg, 130 mg, 120 mg, 110 mg, 100 mg, 90 mg, 85 mg, 80 mg, 75 mg, 70 mg, 65 mg, 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, or 15 mg, within a fixed liquid dosage volume, for example, in a volume of about 1.0 mL to about 100 mL, or for example from about 10 mL to about 100 mL per unit dose. In another embodiment, the amount of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered in an amount of 190 mg, 180 mg, 170 mg, 160 mg, 150 mg, 140, mg, 130 mg, 120 mg, 110 mg, 100 mg, 90 mg, 85 mg, 80 mg, 75 mg, 70 mg, 65 mg, 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, or 15 mg per unit volume (equivalent to a daily dose or a unit dose, or some fraction or part thereof) ranging from about 1 mL to about 100 mL, or from about 10 mL to about 100 mL per dose. In another embodiment, the amount of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered in an amount of about 140 mg, about 80 mg, about 60 mg, about 40 mg, or about 20 mg per unit volume (equivalent to a daily dose or a unit dose, or some fraction or

part thereof) ranging from about 1 mL to about 100 mL, or from about 10 mL to about 100 mL per unit dose. In another embodiment, the amount of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered in a volume ranging from about 1 mL to about 100 mL, or from about 10 mL to about 100 mL per dose (equivalent to a daily dose, or a unit dose, or some fraction or part thereof), wherein each dose contains about 60 mg, or about 40 mg, or about 20 mg of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, for example, an (L)-malate salt (also referred to as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt), and/or the N-1 crystalline forms of the (L)-malate salt (also referred to as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt) of compound 1.

[0049] In these and other embodiments, the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof, is administered orally once daily as its free base or as the malate salt as a liquid dosage form, preferably in a daily dose, or a unit dose, or some fraction or part thereof. In a further embodiment, compound 1 is administered as the (L)-malate salt (also referred to as the S-malate salt) or the (D)-malate salt (also referred to as the R-malate salt). In a further embodiment:

- up to and including 150 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 140 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 130 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 120 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 110 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 100 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 95 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 90 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;

- up to and including 85 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 80 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 75 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 70 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 65 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 60 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 55 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 50 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 45 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 40 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 35 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 30 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 25 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 20 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 15 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 10 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered; or

- up to and including 5 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered.
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 50% to about 95% PEG-400 (w/w), and/or from about 1% to about 30% TPGS (w/w), and/or from about 0.5% to about 20% ethanol (w/w).In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 70% to about 90% PEG-400 (w/w), and/or from about 5% to about 20% TPGS (w/w), and/or from about 1% to about 15% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 80% to about 90% PEG-400 (w/w), and/or from about 5% to about 15% TPGS (w/w), and/or from about 1% to about 10% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, about 85% PEG-400 (w/w), and/or about 10% TPGS (w/w), and/or about 5% ethanol (w/w).

[0050] In these and other embodiments, a liquid formulation comprising compound 1 which is administered orally once daily with fasting as its free base or as a malate salt (for example, the (L)-malate salt, which is also referred to as the S-malate salt, or the (D)-malate salt, which is also referred to as the R-malate salt) to a patient in need thereof. In a further embodiment:

- up to and including 150 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 140 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 130 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 120 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;

- up to and including 110 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 100 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 95 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 90 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 85 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 80 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 75 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 70 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 65 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 60 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 55 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 50 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 45 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 40 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 35 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 30 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;

- up to and including 25 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 20 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 15 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered;
- up to and including 10 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered; or
- up to and including 5 mg of compound 1 or a pharmaceutically acceptable salt thereof is administered,
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 50% to about 95% PEG-400 (w/w), and/or from about 1% to about 30% TPGS (w/w), and/or from about 0.5% to about 20% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 70% to about 90% PEG-400 (w/w), and/or from about 5% to about 20% TPGS (w/w), and/or from about 1% to about 15% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 80% to about 90% PEG-400 (w/w), and/or from about 5% to about 15% TPGS (w/w), and/or from about 1% to about 10% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, about 85% PEG-400 (w/w), and/or about 10% TPGS (w/w), and/or about 5% ethanol (w/w).

[0051] In various embodiments, a patient with a solid tumor, for example, a locally advanced or metastatic solid tumor, may be treated with compound 1, or a pharmaceutically acceptable salt thereof, as a liquid formulation containing 140 mg, 80 mg, 60 mg, 40 mg, or 20 mg of compound 1, which is administered orally once daily with fasting as its free base or

as a malate salt (for example, the (L)-malate salt, which is also referred to as the S-malate salt, or the (D)-malate salt, which is also referred to as the R-malate salt).

[0052] In various embodiments, a patient with a solid tumor, for example, a locally advanced or metastatic solid tumor, may be treated with cabozantinib (S)-malate, which is administered orally once daily with fasting as a liquid dosage form comprising cabozantinib (S)-malate.

[0053] In a further embodiment, the cabozantinib (S)-malate is administered in a liquid pharmaceutical composition formulation containing 140 mg, 80 mg, 60 mg, 40 mg, or 20 mg of cabozantinib orally once daily with fasting.In a further embodiment, as shown in Table 1, the cabozantinib (S)-malate is administered in a liquid pharmaceutical composition which comprises one or more excipients, carriers, or diluents. Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s) or a crystalline form of one of the active compound(s) of formula I or compune 1, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it is crystalline or not. In other words, the carrier should not substantially alter the form of the active compound(s), nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, a compound of formula I or compound I, or a pharmaceutically acceptable salt thereof). For example, in each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 50% to about 95% PEG-400 (w/w),

and/or from about 1% to about 30% TPGS (w/w), and/or from about 0.5% to about 20% ethanol (w/w).

- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 70% to about 90% PEG-400 (w/w), and/or from about 5% to about 20% TPGS (w/w), and/or from about 1% to about 15% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, from about 80% to about 90% PEG-400 (w/w), and/or from about 5% to about 15% TPGS (w/w), and/or from about 1% to about 10% ethanol (w/w).
- In each of the aforementioned examples, the amount of compound 1 or a pharmaceutically acceptable salt thereof is admixed with one or more carriers to prepare an oral formulation containing, for example, about 85% PEG-400 (w/w), and/or about 10% TPGS (w/w), and/or about 5% ethanol (w/w).

[0054] Suitable carriers include, but are not limited to, water, saline, aqueous dextrose, glycerol, ethanol, and the like; solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, and dimethylformamide; oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0055] The liquid pharmaceutical compositions of this disclosure may be prepared by methods know in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990).

[0056] Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of

this disclosure may also contain minor amounts of auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylated hydroxytoluene. The pharmaceutical compositions generally contain about 0.5% to about 99.5% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99.5% to 0.5% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 1% and about 75% by weight of active compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed herein.

[0057] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., one or more compound(s) of this disclosure, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, polyethylene glycol (PEG), ethanol, and the like; and further comprising solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0058] Suspensions, in addition to the active compounds, can contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol, and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

[0059] **Table 2. An example of a liquid formulation containing cabozantinib (S)-malate.**

Ingredient	Theoretical Quantity (mg/unit dose)		
	20-mg Dose	40-mg Dose	60-mg Dose
Cabozantinib (S)-malate	25.34	50.68	76.02
Polyethylene glycol 400 (PEG 400)	2,934.88	5,869.77	8,804.65
d-α-tocopheryl polyethylene glycol succinate (TPGS)	345.28	690.56	1,035.84
Ethanol	172.64	345.28	517.92
Flavorings	3.45	6.91	10.36
Total	3,481.60	6,963.19	10,444.79

[0060] In a further embodiment, the cabozantinib (S)-malate is administered orally once daily.

[0061] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 140 mg.

[0062] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 120 mg.

[0063] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 80 mg.

[0064] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 60 mg.

[0065] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 40 mg.

[0066] In a further embodiment, the amount of cabozantinib (S)-malate that is administered orally once daily is 20 mg.

[0067] In a further embodiment, the cabozantinib (R)-malate is administered orally once daily.

[0068] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 140 mg.

[0069] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 120 mg.

[0070] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 80 mg.

[0071] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 60 mg.

[0072] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 40 mg.

[0073] In a further embodiment, the amount of cabozantinib (R)-malate that is administered orally once daily is 20 mg.

[0074] In another embodiment, compound 1 is administered orally as its free base or a malate salt (for example, the (L)-malate salt, which is also referred to as the S-malate salt, or the (D)-malate salt, which is also referred to as the R-malate salt) once daily in a liquid pharmaceutical composition as provided in the following Table 3.

[0075] **Table 3. An example of a liquid formulation containing cabozantinib (S)-malate.**

Ingredient	(% w/w)
Compound 1	0.73

Ingredient	(% w/w)
Polyethylene glycol 400 (PEG 400)	84.30
d-α-tocopheryl polyethylene glycol succinate (TPGS)	9.92
Ethanol	4.96
Flavorings	0.10
Total	100

[0076] In another embodiment, compound 1 is administered orally as its free base or a malate salt ((L)-malate salt (also referred to as the S-malate salt), or the (D)-malate salt (also referred to as the R-malate salt)) once daily in a liquid pharmaceutical composition as provided in the following table 4.

[0077] **Table 4. An example of a liquid formulation containing cabozantinib (S)-malate.**

Ingredient	Theoretical Quantity (mg/unit dose)
Compound 1	175.00
Polyethylene glycol 400 (PEG 400)	20,268.53
d-α-tocopheryl polyethylene glycol succinate (TPGS)	2,384.53
Ethanol	1,192.27
Flavorings	23.85
Total	24,044.18

[0078] In another embodiment, compound 1 is administered orally as its free base or a malate salt ((L)-malate salt (also referred to as the S-malate salt), or the (D)-malate salt (also referred to as the R-malate salt)) once daily as a liquid dose as provided in the following table 5.

[0079] **Table 5. An example of a liquid formulation containing cabozantinib (S)-malate.**

Ingredient	Function	% w/w
Cabozantinib (S)-malate	Active Ingredient	0.73
Polyethylene glycol 400 (PEG 400)	Solubility Enhancer	84.30
d-α-tocopheryl polyethylene glycol succinate (TPGS)	Solubility Enchancer and Stabilizer	9.92
Ethanol	Solvent	4.96
Cinnamon Flavoring	Taste masking agent	0.10
Total		100

[0080] Any of the liquid dosage formulations provided above can be adjusted according to the dose of compound 1 or a pharmaceutically acceptable salt thereof desired. Thus, the amount of each of the formulation ingredients can be proportionally adjusted to provide a liquid formulation containing various amounts of compound 1 or a pharmaceutically acceptable salt thereof as provided in the previous paragraphs. In another embodiment, the formulations can contain 20, 40, 60, or 80 mg of compound 1 or a pharmaceutically acceptable salt thereof.

[0081] Exemplary Administration Of The Liquid Pharmaceutical Composition And Treatment of Solid Tumors

[0082] Through potent inhibition of RTKs including MET, VEGFR, and AXL, cabozantinib has demonstrated clinical activity as a single agent in both advanced UC and RCC.

[0083] Objectives: The primary objectives of the study were: (1) to determine the time course for excretion of ^{14}C radioactivity in urine and feces following a single 175 mg oral dose of XL184 (L-malate salt) containing 100 μCi [14C]-XL184; (2) to determine the recovery of ^{14}C radioactivity as a percentage of the administered dose; (3) to determine the percentage of ^{14}C radioactivity present as XL184 in plasma and urine at selected time points following administration of the study drug; and (4) to assess the safety of a single dose of 175 mg of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184 in healthy male subjects. The secondary objectives of the study were: (1) to determine the plasma pharmacokinetics of ^{14}C radioactivity and XL184 in healthy male subjects following a single oral dose of study drug; (2) to determine the percentage of ^{14}C radioactivity associated with erythrocytes in whole blood over time; and (3) to estimate the amount and probable structure of any significant metabolites or degradation products of XL184 in plasma and urine.

[0084] The following PK objectives listed above will not be addressed in this example:

[0085] Primary objective (3): to determine the percentage of ^{14}C radioactivity present as XL184 in plasma and urine at selected time points following administration of the study drug;

[0086] Secondary objective (3): to estimate the amount and probable structure of any significant metabolites or degradation products of XL184 in plasma and urine.

[0087] The study was completed as planned.

[0088] Methodology: This was an open-label, single-dose, single-center, mass balance, Phase 1 study in healthy male volunteers. There were two study periods: a Screening Period, during which subjects underwent assessments to determine their eligibility for the study, and an On-study Period, which started on Day -1 ('check-in' day) when the subject was admitted

to the Celerion clinic. Subjects received a single calculated oral dose intended to contain a total of 175 mg of XL184 (L-malate salt) and 100 μCi of ^{14}C at Hour 0 on Day 1; initially they were to remain in the clinic through to the completion of all scheduled post-dose procedures on the morning of Day 28. Alternatively, if scintillation counts were available, subjects, on an individual basis, could be discharged prior to Day 28 if either of the following conditions were met: (1) ≥ 90% of the administered radioactivity was recovered in the urine and feces (accounting for radioactivity in vomitus if applicable); or (2) the daily total excreted radioactivity was 1% or less of the administered dose on 2 consecutive days and ≥ 85% of the administered radioactivity had been recovered. However, subjects who were discharged from the clinic before Day 28 were required to return to the clinic for all remaining scheduled pharmacokinetic blood sampling and the Day 28 safety assessments. Subjects not meeting radioactivity release criteria by Day 28 could be asked to remain confined in the clinic or continue collection of urine and feces at home (returning samples to the clinic daily) for up to an additional 7 days (through to Day 35). Due to the fact that by Day 35 subjects had still not met release criteria, subjects were given the option of withdrawing from the study or completing the additional 14-day collection period (either in the clinic or as a daily visitor) with urine and feces collections and daily adverse event (AE) inquiries. All urine and fecal collections for all subjects stopped following the conclusion of the Day 49 scheduled events regardless of percentage of total radioactive dose recovered.

[0089] Number of subjects (planned and analyzed): 8 planned and 8 analyzed

[0090] Diagnosis and main criteria for eligibility: Healthy male adults, aged 19 to 55 years of age, with screening and check in amylase or lipase levels below the upper limit of normal, a minimum of one bowel movement a day, and no evidence of urinary obstruction or difficulty in voiding urine at screening.

[0091] Test product, dose and mode of administration, and batch numbers: XL184 (L-malate salt) containing [^{14}C]-XL184 (100 μCi dose) was prepared as a dosing solution. Each dosing solution was analyzed for radioactivity content (scintillation counting), radiochemical purity, and XL184 concentration. A single dose oral solution was administered at Hour 0 on Day 1 by the clinic staff. The dose was given via the scintillation vial. Following dosing, the scintillation vial was rinsed 3 times with room temperature distilled water, and the rinsate was administered to the subject. Residual radioactivity was determined for each dosing vial. The total volume of liquid administered including radiolabelled study drug, rinses, and water given for dosing (in addition to the rinses) was the same for each subject.

[0092] Duration of treatment: Each subject was dosed with a single 175 mg oral solution dose of XL184 (L-malate salt) containing [^{14}C]-XL184 (100 μCi).

[0093] Reference therapy, dose and mode of administration, and batch numbers: Not applicable.

[0094] Criteria for evaluation:

[0095] Efficacy: Not applicable (efficacy was not measured in this study)

[0096] Pharmacokinetics: Serial blood, urine, and feces were collected at specified times following dosing. As data allowed, standard noncompartmental pharmacokinetic parameters, including area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (AUC0-t), area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time 24 hours (AUC_{0-24}), area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time 72 hours (AUC_{0-72}), area under the concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + Ct/kel$, where kel is the terminal elimination rate constant and C_t is the last measurable concentration (AUC_{0-inf}), maximum observed concentration (C_{max}), time of maximum concentration (t_{max}), apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration vs. time curve (k_{el}), and apparent terminal elimination half-life calculated as $ln(2)/k_{el}$ ($t_{½}$) were calculated from radioactivity data in plasma and whole blood, and standard noncompartmental pharmacokinetic parameters, including AUC_{0-t}, AUC_{0-24}, AUC_{0-inf}, C_{max}, t_{max}, k_{el}, and $t_{½}$, were calculated from XL184 and/or metabolite concentrations in plasma.

[0097] As data allowed, pharmacokinetic parameters, including urine concentration (Curine), amount excreted during each collection interval, calculated as C_{urine} x urine volume, renal clearance, cumulative amount of dose excreted in urine, percentage recovered in urine over the collection interval, and cumulative percent of dose recovered in urine, were calculated from XL184 and metabolites concentrations in urine. Fecal concentration (C_{feces}), amount excreted during each collection interval, calculated as C_{feces} x fecal weight, cumulative amount of dose excreted in feces, percentage of dose recovered in feces over the collection interval, and cumulative percent of dose recovered in feces, were also calculated from XL184 and metabolites concentrations in feces.

[0098] Mass balance was calculated as the percent of total administered radioactivity recovered in urine and feces. For the purpose of calculating mass balance, the amount of

administered radioactivity was defined as the total radioactivity in the dosing solution minus any radioactivity lost due to emesis (if any occurred), adsorption to the dosing vial, etc.

[0099] To determine the percentage of radioactivity associated with erythrocytes in whole blood over time (ETR; calculated only for time points that whole blood is collected), the following was calculated:

[00100] The amount of ^{14}C radioactivity in plasma versus whole blood, adjusted for the hematocrit, at the specific time points of comparison (ETR=Xe/Xb=1-[Cp * (1-Hct)/Cb], where Xe and Xb stands for amount of radioactivity in erythrocyte or whole blood, respectively. Hematocrit values for Days -1, 2, and 4 were averaged for use in this calculation.

[00101] Safety: Safety evaluations included assessments of AEs, vital signs, electrocardiogram (ECG), laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment were assessed by the investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

[00102] Adverse event terms were standardized using the Medical Dictionary for Regulatory Activities and tabulated by system organ class and preferred term.

[00103] Metabolic Profiling: Details regarding metabolic profiling were prepared under separate cover by QPS, LLC. The results will be reported separately.

[00104] Statistical methods:

[00105] Efficacy: Not applicable (efficacy was not measured in this study).

[00106] Pharmacokinetics: The pharmacokinetic parameters identified above were summarized using descriptive statistics (e.g., mean, median, standard deviation [SD], coefficient of variation (CV), standard error of the mean, geometric mean, minimum, maximum, and sample size). No inferential statistics were calculated. The radiocarbon concentration over each collection period was determined for plasma, whole blood, urine, and feces. To determine the percentage of radioactivity associated with erythrocytes in whole blood over time (calculated only for time points that whole blood is collected) the following was calculated: the amount of radioactivity in plasma versus whole blood, adjusted for the hematocrit, at the specific time points of comparison (ETR=Xe/Xb=1-[Cp * (1-Hct)/Cb], where Xe and Xb stands for amount of radioactivity in erythrocyte or whole blood, respectively. Hematocrit values for Days -1, 2, and 4 were averaged for use in this calculation.

[00107] Safety: AEs and other safety data were summarized and listed as appropriate. Laboratory values were presented to allow evaluation of changes after baseline. No safety data were formally analyzed.

[00108] No interim analyses were performed.

[00109] Summary of Results:

[00110] Disposition of subjects:

[00111] Eight subjects were dosed; one subject was followed for 37 days then withdrew consent while seven subjects were followed for 49 days for urine and feces collection, and one of the seven opted for home collection for the final 14 day extension.

[00112] Pharmacokinetic results:

[00113] Radioactivity recovery

[00114] A summary of cumulative recovery of total radioactivity (as percent of dose) in the urine and feces following a single 175 mg oral administration of XL184 (L-malate salt) containing [^{14}C] XL184 (100 μCi) to the healthy male subjects is presented in the following table.

[00115] Summary (mean ± SD and %CV) of cumulative recovery of total radioactivity (as percent of dose) in urine and feces following a single 175 mg oral administration of XL184 (L-malate salt) containing [^{14}C] XL184 (100 μCi) to healthy male subjects as shown below in Table 6.

[00116] **Table 6. Cumulative recovery of total radioactivity.**

Cumulative Recovery of Total Radioactivity (as Percent of Dose) (n=8)		
Urine	**Feces**	**Total**
27.29±4.65 (17 %)	53.79±4.52 (8%)	81.09±1.56 (2%)

[00117] The mean recovery of radioactivity of 81.09% was achieved within 48 days, and the radioactivity was mainly eliminated in feces (53.79%) and the remainder in urine (27.29%). Less than 1% total mean radioactivity was recovered in feces and urine after Day 28 post dose.

[00118] Radioactivity in plasma and whole blood

[00119] A summary of plasma and whole blood pharmacokinetic parameters for total radioactivity following a single 175 mg oral administration of XL184 (L-malate salt)

containing [^{14}C] XL184 (100 μCi)) to healthy male subjects is presented in the following table.

[00120] Summary (mean ± SD and %CV) of plasma and whole blood pharmacokinetic parameters for total radioactivity following a single 175 mg oral administration of XL184 (L-malate salt) containing [^{14}C] XL184 (100 μCi) to healthy male subjects as shown below in Table 7.

[00121] Table 7. Plasma and whole blood pharmacokinetic parameters for total radioactivity following a single 175 mg oral administration of XL184

Parameters	Plasma	Whole Blood	%Ratio of Plasma to Whole Blood
C_{max}, ngEq/mL	2000±429 (21)	1200±243 (20)	167±12.4 (7)
t_{max}, h[a]	2.00 (1.00, 4.00)	2.00 (1.98, 2.00)	NA
AUC_{0-t}, h·ngEq/mL	259000±42700 (16)	54100±10300 (19)	487±73.3 (15)
AUC_{0-24}, h·ngEq/mL	31400±6380 (20)	19600±3780 (19)	160±6.65 (4)
AUC_{0-72}, h·ngEq/mL	89700±19000 (21)	54100±10300 (19)	165±11.1 (7)
AUC_{0-inf}, h·ngEq/mL	306000±59500 (19)	NR	NA
k_{el}, 1/h	0.00308±0.00182 (59)	NR	NA
$t_{1/2}$, h	269±93.2 (35)	NR	NA

[a]: median (range); NR: Not Reportable (since AUC_{0-t} / AUC_{0-inf} ratio < 0.80); NA: Not Applicable
C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life.

[00122] Following a single oral dose, the peak radioactivity in plasma and whole blood was achieved at approximately 2 hours (median) with a mean C_{max} of 2000 and 1200 ngEq/mL, respectively. The mean elimination half-life value for the total radioactivity in plasma was 269 hours. The mean values of systemic exposures (AUC_{0-24} and AUC_{0-72}) in plasma were around 1.6 times higher than those in whole blood.

[00123] Radioactivity present in erythrocytes and whole blood

[00124] The percent total mean radioactivity concentration present in erythrocytes relative to whole blood ranged from 0.174 ± 4.51 to 12.3 ± 3.71 within 72 hours after single dosing, indicating that radioactivity was present primarily in plasma and not markedly associated with red blood cells.

[00125] Pharmacokinetic parameters of XL184 and its metabolites in plasma

[00126] XL184 and metabolites XL184 half-dimer, XL184-N-oxide, XL184-sulfate, and para fluoroaniline (p-FA) were measured in plasma samples from healthy male subjects

following a single 175 mg oral administration of XL184 containing [^{14}C]XL184 (100 μCi) by a validated LC/MS/MS method. The p-FA concentrations were below the lower limit of quantification at all time points for all subjects. A summary of plasma pharmacokinetic parameters for XL184 and metabolites XL184 half-dimer, XL184-N-oxide, and XL184 sulfate is presented in the following table.

[00127] Summary (mean ± SD, and %CV) of plasma pharmacokinetic parameters for XL184 and selected metabolites following a single 175 mg oral administration of XL184 (L malate salt) containing [^{14}C] XL184 (100 μCi) to healthy male subjects determined by a validated LC/MS/MS method as shown below in Table 8.

[00128] Table 8. Plasma pharmacokinetic parameters for XL184 and selected metabolites following a single 175 mg oral administration of XL184

Parameters	XL184	XL184-Half-Dimer	XL184-N-Oxide	XL184-Sulfate
C_{max}, ng/mL	1250±238 (19)	52.9±17.3 (33)	118±33.7 (28)	236±66.7 (28)
T_{max}, h[a]	1.49 (1.00, 3.00)	18.99 (5.00, 24.10)	13.50 (2.00, 24.30)	24.00 (3.00, 48.00)
AUC_{0-24}, h·ng/mL	14300±2600 (18)	1080±341 (32)	2030±682 (34)	3970±1350 (34)
AUC_{0-72}, h·ng/mL	35000±6770 (19)	3120±976 (31)	5610±1940 (35)	12600±4180 (33)
AUC_{0-t}, h·ng/mL	67200±6880 (10)	6540±1680 (26)	10100±3210 (32)	28900±10700 (37)
Ratio[b], %	NA	9.93±3.20 (32)	15.0±3.80 (25)	42.9±14.4 (33)
Ratio[c], %	60.2±7.05 (12)	5.97±1.91 (32)	8.82±1.48 (17)	25.0±6.60 (26)
AUC_{0-inf}, h·ng/mL	68000±6910 (10)	6770±1700 (25)	10300±3170 (31)	29500±10600 (36)
k_{el}, 1/h	0.00712±0.00176 (25)	0.00807±0.00218 (27)	0.00846±0.00256 (30)	0.00859±0.0022 (26)
$t_{1/2}$, h	102±23.3 (23)	91.8±25.4 (28)	89.2±29.2 (33)	86.0±24.3 (28)

[a]: median (range); [b]: ratio of AUC_{0-t} (metabolite)/AUC_{0-t} (parent);
[c]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent+3 measured metabolites); NA: Not Applicable;
C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life.

[00129] The main circulating compound in plasma was XL184, which was rapidly absorbed after oral administration and eliminated relatively slowly. Following a single oral dose, the mean peak concentrations of XL184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate in plasma were achieved at approximately 1.49, 18.99, 13.50, and 24.00 hours (median) with a mean C_{max} of 1250, 52.9, 118 and 236 ng/mL, respectively. The mean estimated elimination half-lives of XL184, XL184-half-dimer, XL184-N-oxide, and XL184-sulfate were 102, 91.8, 89.2, and 86.0 hours, respectively.

[00130] For metabolites XL184-half-dimer, XL184-N-oxide, and XL184-sulfate, the mean metabolite exposure ratios relative to parent XL184 (AUC0-t (metabolite)/ AUC0-t (parent))

were 9.93%, 15.0%, and 42.9%, respectively. Mean exposure ratios for parent and metabolites XL184 half dimer, XL184-N-oxide and XL184-sulfate relative to total exposure (AUC0-t (each analyte)/AUC0-t (parent+3 measured metabolites)) were 60.2% 5.97%, 8.82%, and 25.0%, respectively.

[00131] Safety results:

[00132] There were no deaths, other SAEs, discontinuations due to AEs, or other significant AEs reported during the study. No subject vomited within 4 hours of dosing. Six subjects (75%) reported a total of 36 TEAEs, the majority of which were mild in severity (CTCAE grade 1). The exception was one event of treatment related dizziness, which was moderate (CTCAE grade 2) in severity. Most TEAEs (31/36, 86%) resolved within 1 to 3 days.

[00133] Apart from the preferred terms 'headache' and 'flatulence,' which were both reported in three (37.5%) subjects, all other preferred terms were reported in only one subject each. Five subjects (62.5%) reported TEAEs that were assessed as related to the study treatment.

[00134] There were no clinically significant changes from baseline in any laboratory values. No remarkable on study results were noted for vital signs or ECG evaluations.

[00135] Conclusion: Every attempt was made to keep the subjects in the clinic to obtain 90% recovery of the administered radioactivity.

[00136] Following oral administration of a single 175 mg dose of XL184 (L-malate salt) containing 100 μCi [^{14}C]-XL184, a mean recovery of total radioactivity of 81.09% was achieved within 48 days. Less than 1% total mean radioactivity was recovered in feces and urine after Day 28 post-dose. The radioactivity was mainly eliminated in feces: (53.79%) and the remainder in urine (27.29%). The peak radioactivity in plasma and whole blood was achieved at approximately 2 hours (median) with a mean C_{max} of 2000 and 1200 ngEq/mL, respectively. The elimination half life of the total radioactivity in plasma was determined with a mean value of 269 hours. The mean values of systemic exposures (AUC_{0-24} and AUC_{0-72}) in plasma were around 1.6 times higher than those in whole blood. The mean percent total radioactivity concentrations associated with erythrocytes relative to whole blood indicated that radioactivity was present primarily in plasma and not markedly associated with red blood cells.

[00137] The main circulating compound in plasma was XL184, which was rapidly absorbed after oral administration and eliminated relatively slowly. Following a single oral dose, the mean peak concentrations of XL184 and metabolites XL184-half-dimer, XL184-N-

oxide, and XL184 sulfate in plasma were achieved at approximately 1.49, 18.99, 13.50, and 24.00 hours (median) with a mean C_{max} of 1250, 52.9, 118, and 236 ng/mL, respectively; the mean estimated elimination half-lives were 102, 91.8, 89.2, and 86.0 hours, respectively.

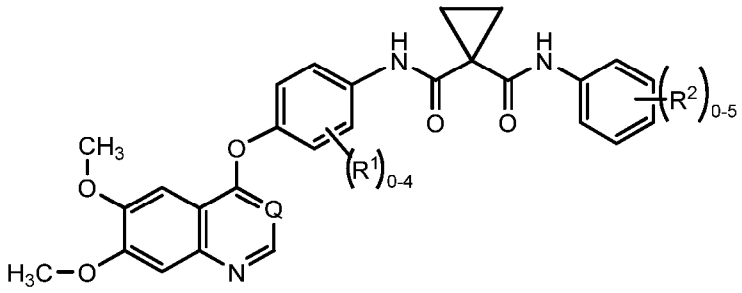
[00138] For metabolites XL184-half-dimer, XL184-N-oxide, and XL184-sulfate, the mean metabolite exposure ratios relative to parent XL184 (AUC0-t (metabolite)/ AUC0-t (parent)) were 9.93%, 15.0%, and 42.9%, respectively. Mean exposure ratios for parent and metabolites XL184 half dimer, XL184-N-oxide, and XL184-sulfate relative to total exposure (AUC0-t (each analyte)/ AUC0-t (parent+3 measured metabolites)) were 60.2%, 5.97%, 8.82%, and 25.0%, respectively.

[00139] The treatment was well tolerated. There were no deaths, other SAEs, discontinuations due to AEs, or other significant AEs. Six subjects (75%) reported a total of 36 TEAEs, the majority of which were mild in severity (CTCAE grade 1); none were severe. Apart from the preferred terms 'headache' and 'flatulence,' which were both reported in three (37.5%) subjects, all other preferred terms were reported in only one subject each. Most TEAEs were transient and resolved within 1 to 3 days. There were no notable clinical laboratory findings, or other safety concerns.

[00140] **Embodiments**

[00141] The invention is further defined by the following non-limiting embodiments.

[00142] Embodiment 1. A liquid pharmaceutical formulation comprising a compound of formula I:



Formula I

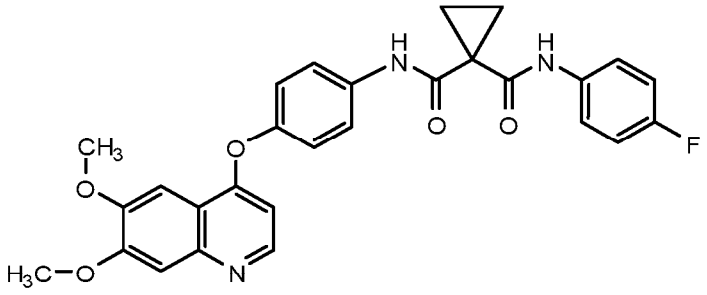
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein:

R^1 is halo;

R^2 is halo; and

Q is CH or N.

[00143] Embodiment 2. The liquid pharmaceutical composition according to embodiment 1, wherein the compound of formula I is compound 1, or a pharmaceutically acceptable salt thereof.



Compound 1

[00144] Embodiment 3. The liquid pharmaceutical composition according to embodiment 2, wherein compound 1 is the L-malate salt (or S-malate salt).

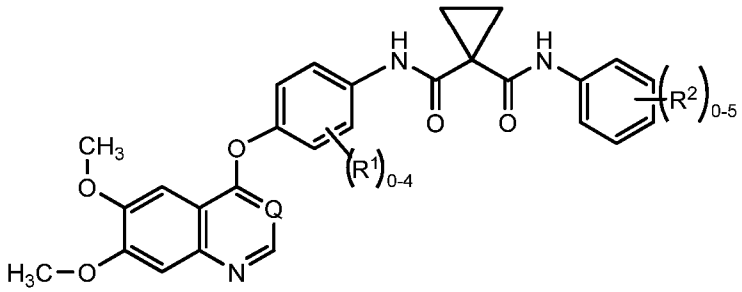
[00145] Embodiment 4. The liquid pharmaceutical composition according to embodiment 2, wherein compound 1 is the D-malate salt (or R-malate salt).

[00146] Embodiment 5. The liquid formulation composition according to any one of embodiments 1-4, wherein the amount of the compound of Formula I or compound 1, or a pharmaceutically acceptable salt thereof present in the liquid formulation, ranges from about 1 mg to about 200 mg.

[00147] Embodiment 6. The liquid pharmaceutical composition according to embodiment 5, wherein the amount of the compound of Formula I or compound 1, or a pharmaceutically acceptable salt thereof present in the liquid formulation is about 60 mg, or about 40 mg, or about 20 mg of the compound of formula I or compound 1, or a pharmaceutically acceptable salt thereof.

[00148] Embodiment 7. The liquid pharmaceutical composition according to embodiment 1, wherein the liquid formulation provides a smaller inter-subject variability in exposure (%CV of about 10% for AUC $_{0\text{-}t}$ and AUC $_{0\text{-}inf}$; reference: Lacy et al, 2015 DMD 43:1190-1207) relative to the tablet formulation ((%CV of about 44% for $AUC_{0\text{-}t}$ and about 46% for $AUC_{0\text{-}inf}$; reference: Nguyen et al, 2016 Anticancer Drugs 27:669-78) upon administration of a single dose of the liquid pharmaceutical composition.

[00149] Embodiment 8. A method of treating locally advanced or metastatic solid tumors, comprising administering a patient in need of such treatment, a liquid pharmaceutical composition comprising a compound of formula I:



Formula I

or a pharmaceutically acceptable salt thereof or a liquid pharmaceutical composition comprising the compound of formula I or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, wherein:

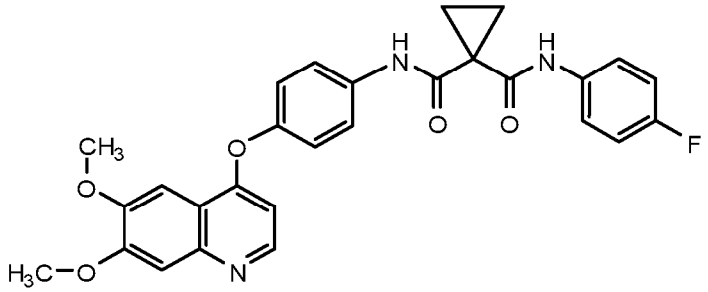
R^1 is halo;

R^2 is halo; and

Q is CH or N,

and wherein administration of a single dose of the liquid pharmaceutical composition to the patient, provides a smaller inter-subject variability in exposure (%CV of about 10% for AUC $_{0\text{-}t}$ and AUC $_{0\text{-}inf}$; reference: Lacy et al, 2015 DMD 43:1190-1207) relative to the tablet formulation ((%CV of about 44% for $AUC_{0\text{-}t}$ and about 46% for $AUC_{0\text{-}inf}$; reference: Nguyen et al, 2016 Anticancer Drugs 27:669-78).

[00150] Embodiment 9. The method according to embodiment 8, wherein the compound of formula I is compound 1, or a pharmaceutically acceptable salt thereof.



Compound 1

[00151] Embodiment 10. The method according to embodiment 9, wherein compound 1 is administered as the L-malate salt (or S-malate salt).

[00152] Embodiment 11. The method according to embodiment 9, wherein compound 1 is administered as the D-malate salt (or R-malate salt).

[00153] Embodiment 12. The method according to any one of embodiments 8-11, wherein the locally advanced or metastatic solid tumors is advanced UC or RCC.

[00154] Embodiment 13. The method according to embodiment 9, wherein compound 1, or a pharmaceutically acceptable salt thereof is administered to the patient in a liquid pharmaceutical composition once daily with fasting in an amount of 100 mg, 95 mg, 90 mg, 85 mg, 80 mg, 75 mg, 70 mg, 65 mg, 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, or 5 mg.

[00155] Embodiment 14. The method according to embodiment 13, wherein compound 1, or a pharmaceutically acceptable salt thereof is administered to the patient in a liquid pharmaceutical composition once daily with fasting in an amount of 60 mg, 40 mg, or 20 mg.

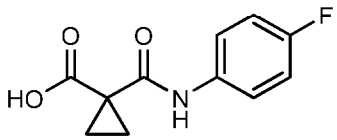
[00156] Embodiment 15. The method according to any one of embodiments 9-14, wherein a complete serological response is observed in patients being treated with the liquid pharmaceutical composition comprising compound 1, or a pharmaceutically acceptable salt thereof.

[00157] Embodiment 16. The method according to any one of embodiments 9-14, wherein a serological partial response is observed in patients being treated with compound 1, or a pharmaceutically acceptable salt thereof.

[00158] Embodiment 17. The method according to any one of embodiments 9-14, wherein stable disease is observed in patients being treated with compound 1, or a pharmaceutically acceptable salt thereof.

[00159] **Preparation of Compound 1**

Preparation of 1-(4-Fluorophenylcarbamoyl)cyclopropanecarboxylic acid (Compound A-1)



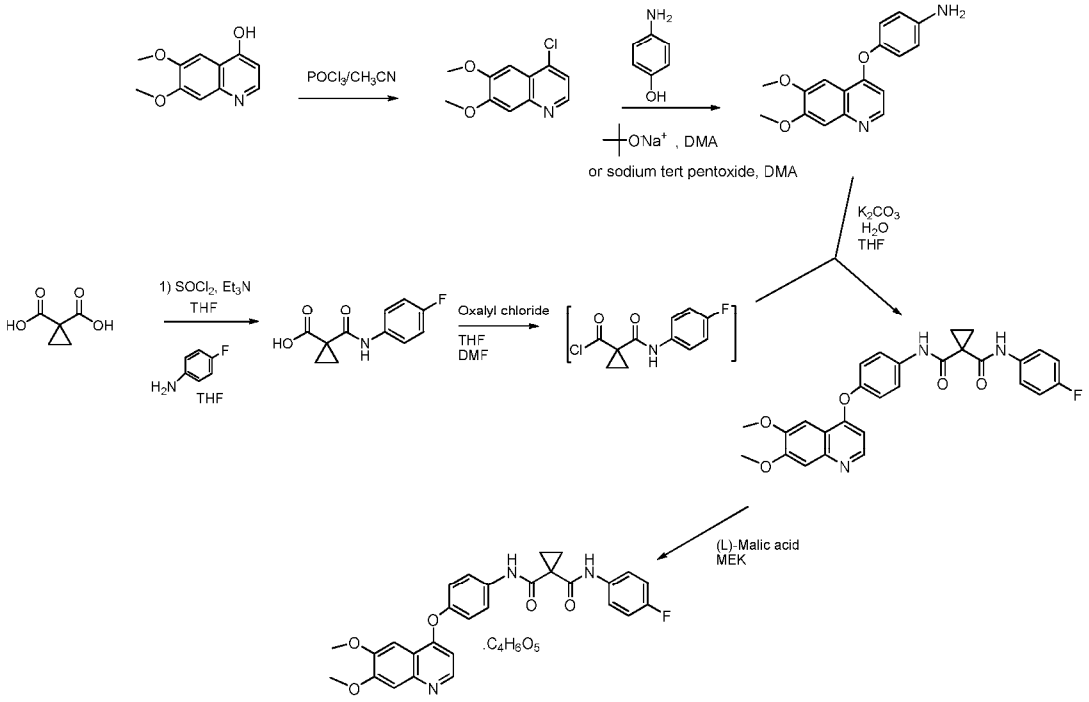
[00160] The starting 1,1-cyclopropanedicarboxylic acid was treated with thionyl chloride (1.05 equivalents) in approximately 8 volumes of isopropyl acetate at 25 °C for 5 hours. The resulting mixture was then treated with a solution of 4-fluoroaniline (1.1 equivalents) and triethylamine (1.1 equivalents) in isopropyl acetate (2 volumes) over 1 hour. The product slurry was quenched with 5N NaOH solution (5 volumes), and the aqueous phase was discarded. The organic phase was extracted with 0.5N NaOH solution (10 volumes), and the basic extract was washed with heptane (5 volumes) and subsequently acidified with 30% HCl solution to give a slurry. Compound A-1 was isolated by filtration.

[00161] Compound A-1 was prepared on a 1.00 kg scale using 1,1-cyclopropanedicarboxylic acid as the limiting reagent to furnish 1.32 kg of Compound A-1 (77% isolated yield; 84% mass balance) with 99.92% purity (HPLC) and 100.3% assay.

[00162] **Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound 1) and the (L)-malate salt thereof**

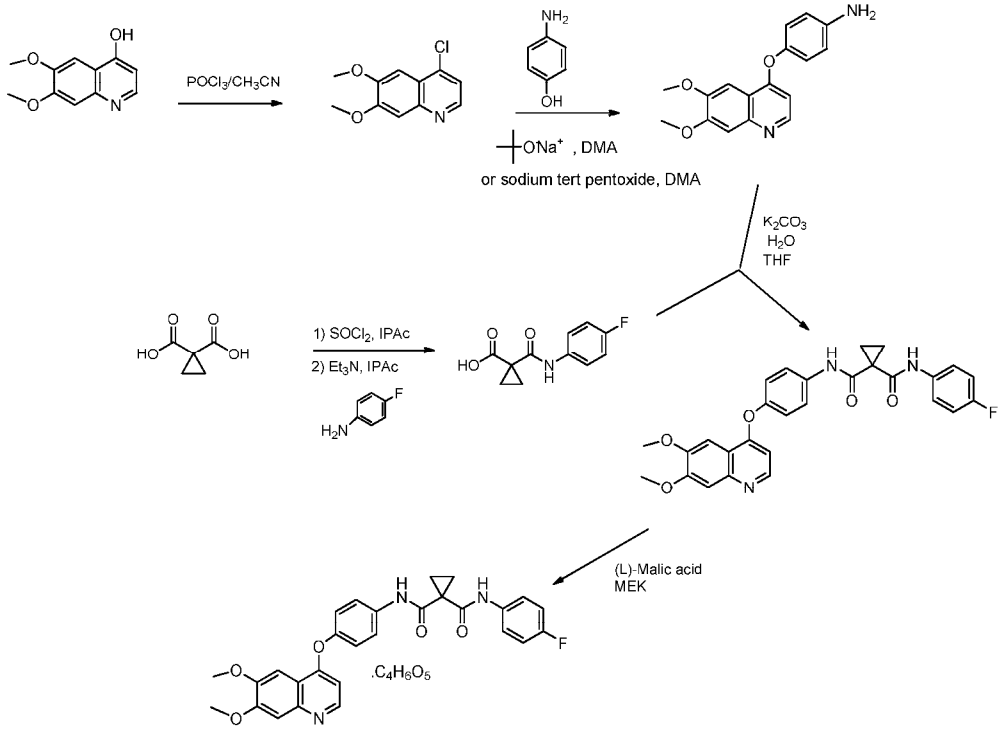
[00163] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1.

Scheme 1



[00164] Another synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 2.

Scheme 2



[00165] **Preparation of 4–Chloro–6,7–dimethoxy–quinolone**

[00166] A reactor was charged sequentially with 6,7–dimethoxy–quinoline–4–ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained, as measured by in-process high-performance liquid chromatography [HPLC] analysis. The reaction mixture was cooled to approximately 2 to 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 to 25 °C, and phases were separated. The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg), and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated, and the organic phase was concentrated by vacuum distillation with the removal of solvent

(approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged, and the temperature of the mixture was adjusted to – 20 to – 25 °C and held for 2.5 hours resulting in solid precipitate, which was then filtered, washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound (35.6 kg).

[00167] Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[00168] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg), and DMA (167.2 kg) at 20 – 25 °C. This mixture was then heated to 100 – 105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15 to 20 °C, and water (pre-cooled, 2 to 7 °C, 587 L) was charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg), and finally washed with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1 hour, then cooled to 0 to 5 °C, and aged for approximately 1 hour, after which time the solid was filtered, washed with THF (147.6 kg), and dried on a filter under vacuum at approximately 25 °C to yield 4–(6, 7 –dimethoxy–quinoline–4–yloxy)–phenylamine (34.0 kg).

[00169] Alternative Preparation of 4–(6, 7 –Dimethoxy–quinoline–4–yloxy)–phenylamine

[00170] 4-chloro-6,7-dimethoxyquinoline (34.8 kg), 4-Aminophenol (30.8 kg), and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 weight percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105 to 115 °C for approximately 9 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (less than 2% starting material remaining), the reactor contents were cooled at 15 to 25 °C, and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 25 °C. The crude product was collected by

filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

[00171] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used, and the reaction temperature was increased from 110 to 120 °C. In addition, the cool down temperature was increased to 35 to 40 °C, and the starting temperature of the water addition was adjusted to 35 to 40 °C, with an allowed exotherm to 45 °C.

[00172] Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[00173] Oxalyl chloride (12.6 kg) was added to a solution of 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

[00174] Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride

[00175] A reactor was charged with 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarboxylic acid (35 kg), DMF (344 g), and THF (175kg). The reaction mixture was adjusted to 12 to 17 °C, and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12 to 17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

[00176] Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[00177] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20 to 25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

[00178] Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide

[00179] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by THF (412.9 kg). To the reaction mixture was charged a solution of K_2CO_3 (48.3 kg) in water (169 kg). The acid chloride solution of described in the Alternative Preparation of 1–(4–Fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine while maintaining the temperature between 20 to 30 °C over a minimum of two hours. The reaction mixture was stirred at 20 to 25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30 to 25 °C, and the mixture was agitated. The agitation was stopped, and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added water (804 kg). The reaction was left stirring at 15 to 25 °C for a minimum of 16 hours.

[00180] The product precipitated. The product was filtered and washed with a mixture of water (179 kg) and THF (157.9 kg) in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in THF (285.1 kg). The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30 to 35 °C for approximately 30 minutes. Water (456 kg) was then added to the solution, as well as SDAG-1 ethanol (20 kg, ethanol denatured with methanol over two hours). The mixture was agitated at 15 to 25 °C for at least 16 hours. The product was filtered and washed with a mixture of water (143 kg and 126.7 kg THF (143 kg) in two portions. The product was dried at a maximum temperature set point of 40 °C.

[00181] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10 to 15 °C. The recrystallization temperature was changed from 15 to 25 °C to 45 to 50 °C for 1 hour and then cooled to 15 to 25 °C over 2 hours.

[00182] Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, cabozantinib (L) malate salt

[00183] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor, and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C, and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–

amide (4–fluoro–phenyl)–amide (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg), and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF < 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours, resulting in solid precipitate which was filtered, washed with MEK (448 kg), and dried under vacuum at 50 °C to afford the title compound (45.5 kg).

[00184] Alternative Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt

[00185] Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (47.9 kg), L-malic acid (17.2 kg), methyl ethyl ketone (658.2 kg), and water (129.1 kg) were charged to a reactor, and the mixture was heated 50 to 55 °C for approximately 1 to 3 hours and then at 55 to 60 °C for an additional 4 to 5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20 to 25 °C and vacuum distilled with a vacuum at 150 to 200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558 to 731 L.

[00186] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy–quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide by charging methyl ethyl ketone (159.9 kg) to give a total volume of 880 L. An additional vacuum distillation was carried out by adjusting methyl ethyl ketone (245.7 kg). The reaction mixture was left with moderate agitation at 20 to 25 °C for at least 24 hours. The product was filtered and washed with methyl ethyl ketone (415.1 kg) in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

[00187] In an alternative procedure, the order of addition was changes so that a solution of L-malic acid (17.7 kg) dissolved in water (129.9 kg) was added to Cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

[00188] Example 1. Phase I Study of Mass Balance Study Of Cabozantinib (L-malate salt) Following a Single 175 mg Oral Administration of [^{14}C]- Cabozantinib (100 μCi) in healthy male subjects

[00189] 1. BACKGROUND AND RATIONALE

[00190] 1.1 Background

[00191] Multi-targeted tyrosine kinase inhibitors (TKIs) and checkpoint inhibiting immunotherapies represent two systemic modalities that have been instrumental in the recent advancements of anticancer treatment over the past several years. Both classes of therapies have demonstrated broad clinical effects leading to new approved treatment options across multiple tumor types including renal cell carcinoma (RCC), urothelial carcinoma (UC), melanoma, non-small-cell lung cancer (NSCLC), and others. The success of these therapy types as single agents with distinct mechanisms of action has naturally led to interest in evaluating combinations of TKIs with checkpoint inhibitors in search of further, possibly synergistic, anticancer clinical effects.

[00192] XL184 is a new chemical entity that inhibits multiple receptor tyrosine kinases implicated in tumor growth and neoangiogenesis. The primary targets of XL184 are hepatocyte growth factor receptor protein (MET), vascular endothelial growth factor receptor 2 (VEGFR2), and rearranged during transfection (RET) proto-oncogene.

[00193] XL184 is orally bioavailable as demonstrated by pharmacokinetic (PK) studies in rodent and non-rodent models. In *in vivo* target modulation studies, administration of XL184 to mice resulted in dose-dependent inhibition of MET, VEGFR2, and RET (Yakes, et al. 2011). Immunohistochemistry studies demonstrate rapid effects on the endothelium, vascular breakdown, and tumor cell death within 24 hours after administration of XL184. This effect translates into significant tumor growth inhibition after XL184 treatment in multiple tumor models. Additionally, in the models tested (human medullary thyroid cancer, human breast cancer, and rat glioma), marked tumor regression was observed.

[00194] Clinical activity with the use of XL184 in a variety of tumor settings has been reported and the drug is currently being developed for use in oncology.

[00195] 1. Introduction

[00196] The pharmacokinetic (PK) and statistical analyses of plasma, whole blood, urine and feces concentration, and total radioactivity data were performed and reported in the Clinical Pharmacokinetic Report for the Study XL184-012.

[00197] 2. Study Objectives

[00198] The objectives of the study were:

[00199] (1) To determine the time-course for excretion of ^{14}C radioactivity in urine in healthy male subjects following a single oral dose of the study drug.

[00200] (2) To determine the time-course for excretion of ^{14}C radioactivity in feces in healthy male subjects following a single oral dose of the study drug.

[00201] (3) To determine the recovery of ^{14}C radioactivity as a percentage of administered dose.

[00202] (4) To determine the plasma pharmacokinetics (PK) of ^{14}C radioactivity in healthy male subjects following a single oral dose of the study drug.

[00203] (5) To determine the whole blood pharmacokinetics (PK) of ^{14}C radioactivity in healthy male subjects following a single oral dose of the study drug.

[00204] (6) To determine the percentage of ^{14}C radioactivity associated with erythrocytes in whole blood over time.

[00205] (7) To determine the plasma pharmacokinetics (PK) of XL184 and its metabolites by LC/MS/MS in healthy male subjects following a single oral dose of the study drug.

[00206] (8) To determine the urine pharmacokinetics (PK) of XL184 and its metabolites in healthy male subjects using a radio-quantitative method following a single oral dose of the study drug.

[00207] (9) To determine the feces pharmacokinetics (PK) of XL184 and its metabolites in healthy male subjects using a radio-quantitative method following a single oral dose of the study drug.

[00208] (10) To determine the plasma pharmacokinetics (PK) of XL184 and its metabolites in healthy male subjects using a radio-quantitative method following a single oral dose of the study drug.

[00209] 3. INVESTIGATION PLAN

[00210] 3.1 Summary of Study Design

[00211] The clinical phase of the study was conducted from 15 March 2011, through 07 June 2011. This study was designed as an open-label, single-dose, mass balance study conducted in 8 healthy male subjects at one study center in the US. Additional subjects would be enrolled only to replace any dosed subjects who drop out of the study prior to recovery of at least 85% of the radioactive dose in the subject's vomitus, urine, and feces. The primary endpoints of the study were time course for excretion of ^{14}C radioactivity in urine and feces; the recovered percentage of the total dose of ^{14}C radioactivity; and the percentage of ^{14}C radioactivity present as XL184 in plasma and whole blood at selected time points.

[00212] Subjects received a single calculated oral dose intended to contain a total of 175 mg of XL184 (L-Malate Salt) containing 100 μCi of ^{14}C.

[00213] 3.1.1 Identity of Investigational Product(s)

Name: XL184

Active Compound:	XL184
Activity:	Cancers
Route of Administration:	Oral
Dose/Solution:	175 mg XL184 (L-Malate Salt) Containing ^{14}C XL184 (100 μCi)

[00214] 3.2 Pharmacokinetic Evaluations and Metabolic Profiling Samples

[00215] 3.2.1 Blood Sample Collections

[00216] Plasma

[00217] Blood samples for plasma for analysis of total radioactivity (10 mL each) and for PK analysis of XL184 and/or metabolite concentrations (3 mL each) were collected predose (within the 15 minutes prior to dose) and at 0.5, 1, 2, 3, 4, 5, 8, 14, 24, 48, 72, 120, 144, 168, 240, 336, 408, 504, and 648 hours post-dose. Blood samples for plasma for possible metabolic profiling (10 mL each) were collected pre-dose (within the 15 minutes prior to dose) and at 0.5, 1, 2, 3, 4, 5, 8, 14, 24, 72, 168, 336, 504, and 648 hours post-dose. Prior to study initiation, the Celerion Scintillation Laboratory and the laboratory performing the XL184/metabolite analysis and metabolic profiling (QPS, LLC) supplied to the Celerion clinic complete written instructions for collection, aliquot volume required for analysis, handling, processing, and shipping (if applicable) of samples. All samples collected for radioactivity analysis were analyzed for total radioactivity.

[00218] If radioactivity was present in the plasma samples, individual samples at selected time points were analyzed for XL184 and/or metabolites content and metabolic profiling as determined by the sponsor.

[00219] Whole Blood

[00220] Blood samples (4 mL) for whole blood analysis of total radioactivity were collected within 15 minutes pre-dose and at 1, 2, 4, 8, 14, 24, and 72 hours post-dose. Prior to study initiation, the Celerion Scintillation Laboratory supplied to the Celerion clinic complete written instructions for collection, handling, and processing of samples. Samples collected were used to determine the percentage of radioactivity associated with erythrocytes in whole blood over time (calculated only for time points that whole blood was collected).

[00221] 3.2.2 Urine

[00222] Urine samples were collected for the analysis of total radioactivity and for possible analysis for XL184 and/or metabolites and possible metabolic profiling. Subjects were asked to empty their bladders within approximately 60 minutes prior to dosing for the

pre-dose sample. Samples were collected during the 0 to 8 hours and 8 to 24 hours post-dose intervals, and then continuing in 24-hour intervals through Day 49. For subjects who met early release criteria, sampling could cease upon discharge from the clinic. Six subjects were contained in the clinic through 1152 hours (Day 49). One subject was released from the clinic following the 816 hour interval (Day 35) collection and was allowed to home-collect excreta through 1152 hours. One subject was released from the clinic following the 864 hour interval (Day 37) collection and no longer provided excreta samples.

[00223] Urine was refrigerated during the collection intervals. Subjects were instructed to urinate at the end of each collection period, if possible. The total volume collected for each interval was recorded. At the end of each collection interval, the urine was mixed to suspend any sediment and the appropriate aliquots were removed. After preparing the necessary aliquots, the remaining samples were destroyed.

[00224] Prior to study initiation, the Celerion Scintillation Laboratory and the laboratory performing the XL184/metabolite analysis and metabolic profiling (QPS, LLC) supplied to the Celerion clinic complete written instructions for collection, aliquot volume required for analysis, handling, processing, and shipping (if applicable) of samples. All samples collected for radioactivity were analyzed. If radioactivity was present in the urine samples, individual samples at selected time points might be analyzed for XL184 and/or metabolites content and metabolic profiling as determined by the sponsor.

[00225] 3.2.3 Feces

[00226] Subjects were asked to bring a pre-dose stool sample with them at check-in (produced within 24 hours of check-in). Stools produced between subject check-in and dosing were collected for the pre-dose sample as well, and the sample produced nearest to dosing was used as the pre-dose sample. Post-dose stools were collected in 24-hour intervals through the morning of Day 49. For subjects who met early release criteria, sampling could cease upon discharge from the clinic. Six subjects were contained in the clinic through 1152 hours (Day 49). One subject was released from the clinic following the 816 hour interval (Day 35) collection and was allowed to home-collect excreta through 1152 hours. One subject was released from the clinic following the 864 hour interval (Day 37) collection and no longer provided excreta samples.

[00227] For each subject, multiple fecal specimens from each 24-hour interval were combined into a pre-weighed wide mouth polypropylene/polyethylene container and appropriately labeled. For each interval, the fecal sample was weighed to determine the final

fecal weight. Each sample was homogenized into a slurry (approximately 20% suspension in water) from which the necessary aliquots were taken.

[00228] Prior to study initiation, the Celerion Scintillation Laboratory and the laboratory performing the XL184/metabolite analysis and metabolic profiling (QPS, LLC) supplied to the Celerion clinic complete written instructions for collection, aliquot volume required for analysis, handling, processing, and shipping (if applicable) of samples. All samples collected for radioactivity were analyzed. If radioactivity was present in the fecal samples, individual samples at selected time points might have been analyzed for XL184 and/or metabolites content and metabolic profiling as determined by the sponsor.

[00229] 3.2.4 Emesis

[00230] If emesis occurred within 4 hours following dosing, it was collected (if possible) and stored for potential scintillation counting. The vomitus should have been weighed (the weight recorded in the CRF); labeled with subject number, time, and date; and placed in a freezer set at -20°C ± 10°C until it could be analyzed for radioactivity.

[00231] If emesis occurred within 4 hours of dose administration, the subject was replaced and no re-dosing of the same subject was permitted. If radioactivity recovered in vomitus in such subject was ≥ 85% of total administered radioactivity, the subject would have been discharged. However, if radioactivity recovered in vomitus was < 85% of total administered radioactivity, the radioactivity in urine and feces produced by this subject might have been measured and monitored throughout the study upon discretion of the sponsor. A new subject might have been enrolled in the study to replace such a subject.

[00232] 3.3 Drug Concentration Measurements

[00233] 3.3.1 Scintillation Counting

[00234] The Celerion Scintillation Laboratory, 621 Rose Street, Lincoln, Nebraska, performed sample analysis for radioactivity. All analyses were conducted in accordance with GLP.

[00235] Individual dosing containers (including the dosage form) were analyzed pre-dose and post-dose for radioactivity, with the (post-dose - pre-dose) difference being the administered dose. Whole blood, plasma, urine, feces, and emesis (if applicable) were analyzed for radioactivity content by liquid scintillation counting procedures. Whole blood and fecal samples were dried and oxidized prior to counting. Detailed reports of scintillation counting method and results for total radioactivity accompany the clinical study report.

[00236] 3.3.2 Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) and Radio-quantitative Method for XL184 and/or Metabolite Content

[00237] Plasma concentrations of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, and XL184-Sulfate were measured using a validated LC/MS/MS method by QPS, LLC, 3 Innovation Way, Suite 240, Newark, DE 19711, USA. Detailed reports of the bioanalytical methodologies and results accompany the clinical study report. Analyses of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, and XL184-Sulfate were conducted in accordance with GLP. However, the newly identified metabolite, 6-Demethyl Half-Dimer Sulfate, was measured using a non-validated method by QPS, LLC and was not conducted in accordance with GLP.

[00238] The other minor metabolite in plasma, p-Fluoroaniline, was analyzed by Exelixis using a validated LC/MS/MS method. The values of p-Fluoroaniline concentrations for all the plasma samples were below the lower limit of quantitation (2.0 ng/mL). Therefore, no data will be listed for p-Fluoroaniline concentrations in this study report.

[00239] The newly identified metabolite, 6-Demethyl Half-Dimer Sulfate, was measured using non-validated method by QPS, LLC.

[00240] In addition, the plasma concentration of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, P2, and P7 were determined using a non-GLP radio-quantitative method by QPS, LLC, 3 Innovation Way, Suite 240, Newark, DE 19711, USA. Detailed reports of the radio-quantitative method and results can be found in the DMPK report.

[00241] 3.4 Pharmacokinetic Parameters Estimation

[00242] 3.4.1 Mass Balance and Blood-to-Plasma Distribution

[00243] Mass balance was calculated as the percent of total administered radioactivity recovered in urine and feces. For the purpose of calculating mass balance, the amount of administered radioactivity was defined as the total radioactivity in the dosing solution minus any radioactivity lost due to emesis (if any occurred), adsorption to the dosing cup, etc.

[00244] To determine the percentage of radioactivity associated with erythrocytes in whole blood over time (calculated only for time points where whole blood was collected), the following was calculated: the amount of radioactivity in plasma versus whole blood, adjusted for the hematocrit, at the specific time points of comparison (ETR=Xe/Xb=l-[Cp * (1-Hct)/Cb], where Cp stands for amount of radioactivity in plasma and Cb stands for the amount of radioactivity in blood and Hct stands for hematocrit value. Hematocrit values for Days -l, 2, and 4 were averaged for use in this calculation.

[00245] 3.4.2 Plasma and Whole Blood

[00246] As appropriate, the PK parameters were calculated as data allowed for XL184 and/or metabolite concentrations in plasma and for radioactivity in plasma and whole blood (i.e., nanogram equivalents from radioactivity) using noncompartmental approaches. PK variables were computed using WinNonlin Professional, version 5.2. The definition for each PK variable is listed in the following table. Actual elapsed sampling times relative to [^{14}C]-XL184 (100 μCi) oral administration were used for the estimation of PK metrics.

[00247] **Table 9. PK Variable Definitions.**

C_{max}	Maximum observed concentration
t_{max}	Time of the maximum concentration
AUC_{0-t}	Area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time t, where t was the time of the last measurable concentration (C_t)
AUC_{0-24}	Area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time 24 hours
AUC_{0-72}	Area under the concentration-time curve calculated using linear trapezoidal summation from time zero to time 72 hours
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/k_{el}$, where k_{el} was the terminal elimination rate constant
k_{el}	Apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration vs. time curve
$t_{½}$	Apparent terminal elimination half-life calculated as $ln(2)/k_{el}$
%Ratio of AUC_{met}/AUC_{XL184}	%Ratio of AUC_{met}/AUC_{XL184} = %(AUC_{0-t} of metabolite)/(AUC_{0-t} of XL184)
%Ratio of $AUC_{analyte}/AUC_{XL184+Metabolites}$	%Ratio of $AUC_{analyte}/AUC_{XL184+Metabolites}$ = %(AUC_{0-t} of XL184 or metabolite)/(AUC_{0-t} of XL184 and metabolites)

[00248] The C_{max} and time to peak concentration (t_{max}) were directly determined from the observed blood/plasma concentrations data. AUC_{0-24}, AUC_{0-72}, and AUC_{0-t}, the area under the concentration-time curve from time zero to 24 hours post dose, to 72 hours postdose, and to the time of the last measurable concentration (C_t), were calculated using the linear trapezoidal method.

[00249] The area under the blood/plasma concentration time curve from time zero to 24 hours postdose, to 72 hours postdose, or up to the last quantifiable concentration (AUC_{0-t}) was estimated by numerical integration using the linear trapezoidal rule (Equation 1):

$$AUC_{0-t} = \sum_{i=2}^{n} 0.5 \cdot (C_i + C_{i-1}) \cdot (t_i - t_{i-1}) \quad \text{Eq. 1}$$

where C_i was the blood / plasma concentration at the corresponding sampling time point of 24, 72 hours or t_i, and n was the number of time points up to and including the last quantifiable concentration.

[00250] Estimates of half-life ($t_{1/2}$) were calculated using the following (Equation 2):

$$t_{1/2} = \frac{0.693}{k_{el}} \qquad \text{Eq. 2}$$

where the value of the terminal-phase disposition rate constant (k_{el}) of the apparent phase were determined by a non-compartmental analysis using WinNonlin. A regression analysis was performed on the terminal linear phase of the semi-logarithmic plots of individual blood/ plasma concentration time data. During the analysis, WinNonlin repeated regressions using the last three points with non-zero concentrations, then the last four points, and the last five, etc. Points prior to C_{max} were not used. Points with a value of zero for the dependent variable were excluded. For each regression, an adjusted R^2 was computed:

$$\text{Adjusted } R^2 = 1-(1- R^2)*(n-1)/(n-2) \qquad \text{Eq. 3}$$

where n was the number of data points in the regression, and R^2 was the square of the correlation coefficient. WinNonlin estimates k_{el} using the regression with the largest adjusted R^2, and, if the adjusted R^2 did not improve but was within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points was used. k_{el} had to be positive and calculated from at least three data points.

[00251] If the terminal phase for any individual subject failed to meet the stated criteria, the $t_{1/2}$ were considered to be not reportable.

[00252] The area under the plasma concentration time curve up to time infinity ($AUC_{0\text{-inf}}$) was computed using the following (Equation 4):

$$AUC_{0-\text{inf}} = AUC_{0-t} + \frac{C_t}{k_{el}} \qquad \text{Eq. 4}$$

where C_t was the last measurable concentration.

[00253] 3.5 Some Data Handling Procedures

[00254] If a PK profile did not contain more than five consecutive data points with a quantifiable concentration value, this PK profile was considered not evaluable by the pharmacokineticist.

[00255] Only subjects included in the pharmacokinetic analysis were included in the summary statistics.

[00256] Below *the Quantification Limit (BQL):*

[00257] Plasma, blood, urine, and feces concentrations below quantifiable limits (BQL) were imputed with a value of zero for the calculation of PK metrics.

[00258] *The area under the concentration time curve up to time infinity ($AUC_{0\text{-}inf}$)*

[00259] $AUC_{0\text{-}inf}$ was considered reportable if the following criteria were met:

- $t_{1/2}$ was estimable according to Section [00241].
- $AUC_{0\text{-}t}$ / $AUC_{0\text{-}inf}$ ratio ≥ 0.80.

[00260] If $AUC_{0\text{-}inf}$ for an individual subject fails any of the above criteria, the value was reported as NE or NR, where

- NE: could not be estimated.
- NR: $AUC_{0\text{-}t}$ / $AUC_{0\text{-}inf}$ ratio < 0.80; therefore, $AUC_{0\text{-}inf}$ and $t_{1/2}$ were not reportable.

[00261] *Data Format (significant figures and decimal points):*

[00262] Pharmacokinetic parameters were reported to 3 significant figures for individual parameters and summary statistics, with the exception of t_{max} (2 decimal places) and CV% and N, which were whole numbers (0 decimal places).

[00263] 3.6 Statistical Evaluations of PK parameters

[00264] Descriptive statistics [sample size, mean, standard deviation (SD), standard error of the mean (SEM), minimum, median, maximum, coefficient of variation, and geometric mean] were calculated for those PK parameters identified in the section describing Pharmacokinetic Parameters Estimation. No inferential statistics were calculated.

[00265] 4. PHARMACOKINETICS RESULTS

[00266] 4.1 Data Set Analyzed

[00267] Eight subjects were enrolled and completed the study. No subject was withdrawn from the study and experienced the emesis. The statistical analysis population, therefore, consists of 8 subjects.

[00268] 4.2 Pharmacokinetic Results

[00269] 4.2.1 Mass Balance Results

[00270] The actual total amounts of the dose of XL184 with [^{14}C]-radioactivity for individual subjects are listed in Table 10. The individual cumulative percent excretion of [^{14}C]-radioactivity in the urine and feces based on total radioactivity after a single oral dose administration of XL184 (L-Malate Salt) containing [^{14}C]-XL184 solution in eight healthy male subjects are presented in Table 16 and 17, respectively. The total cumulative percent

recoveries of [^{14}C]-radioactivity in the urine and feces based on total radioactivity after a single 175 mg oral dose administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 formulated as a solution in eight healthy male subjects is listed in Table 19.

[00271] Individual subject urine and feces cumulative excretion of total radioactivity versus time plots following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C] XL184 was tracked.

[00272] Mean (±SD) cumulative excretion versus time plots of total radioactivity in urine and feces following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C] XL184 to healthy male subjects are shown in FIG. 1.

[00273] **Table 10. Dosing Record.**

Subject	XL184 (mg)	Total Radioactivity (μCi)
1444-1010	192.01	104.74
1444-1023	189.97	103.63
1444-1040	191.81	104.63
1444-1042	189.59	103.42
1444-1051	188.35	102.74
1444-1052	187.93	102.51
1444-1057	188.41	102.77
1444-1058	189.57	103.41

[00274] A summary of cumulative recovery of total radioactivity (as percent of dose) in the urine and feces following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C] XL184 to the healthy male subjects is presented in Table 11.

[00275] **Table 11. Summary (Mean ± SD and %CV) of Cumulative Recovery of Total Radioactivity (as Percent of Dose) in Urine and Feces Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to Healthy Male Subjects.**

Cumulative Recovery of Total Radioactivity (as Percent of Dose) (n=8)		
Urine	Feces	Total
27.29±4.65 (17 %)	53.79±4.52 (8%)	81.09±1.56 (2%)

[00276] An average 27.29% (ranged from 19.78% to 34.88% based on Table 19) and 53.79% (ranged from 46.54% to 61.89% based on Table 19) of the dose was excreted in the urine and feces following the oral administration of the 175 mg XL184 containing 100 μCi [^{14}C]-XL184 to eight male healthy volunteers, respectively. An average of 81.09% (ranged from 78.14% to 83.38% based on Table 19) of the dose was excreted in total in the urine and feces through 48 days post dose. Approximately 1% total mean radioactivity was recovered in feces and urine after Day 28 post-dose. In human radiolabel studies, total cumulative recovery of radioactivity in excreta above 80% may be considered acceptable for mass balance evaluation and sufficient recovery of radioactivity. The total recovery was considered satisfactory (81.09%), with a predominant fecal excretion of 53.79% and urine excretion of 27.29%.

[00277] 4.2.2 Pharmacokinetic Results

[00278] 4.2.2.1 Pharmacokinetic Parameters for Total Radioactivity in Plasma and Whole Blood

[00279] The individual and mean plasma and whole blood concentration data for [^{14}C]-radioactivity after single dose administration of 175 mg of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 formulated as a solution in healthy male subjects are presented in Tables 22 and 23, respectively. The individual and mean hematocrit values are listed in Table 22. The individual and descriptive statistics of the percentage of ^{14}C radioactivity associated with erythrocytes in whole blood (ETR) over time are included in Table 26. The individual actual blood sampling times of total radioactivity for plasma and whole blood are listed in Table 27.

[00280] The individual subject ^{14}C total radioactivity in plasma and whole blood and plasma XL184 concentration (by LC/MS/MS method) versus time plots following a single 175 mg oral administration of 175 mg of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 are presented in the figures herein (linear axes) and (semi-logarithmic axes). The individual percentage of ^{14}C radioactivity associated with erythrocytes in whole blood (ETR) over time graphs following a single oral administration of 175 mg of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects are shown in the figures and tables herein.

[00281] The individual subject and descriptive statistics for pharmacokinetic parameters of [^{14}C]-radioactivity in plasma and whole blood are included in Table 26 and Table 27, respectively.

[00282] WinNonlin outputs of pharmacokinetic analyses of total radioactivity in plasma and whole blood data are included in the Figures and Tables herein.

[00283] FIGS. 2 and 3 (linear axes) and FIGS. 4 and 5 (semi-logarithmic axes) illustrate the mean (±SD) ^{14}C total radioactivity in plasma and whole blood and plasma XL184 concentration (by LC/MS/MS method) versus time plots after administration of single 175 mg dose of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 formulated as an oral solution, respectively. FIG. 6 demonstrates the mean (±SD) plots of percentage of ^{14}C radioactivity associated with erythrocytes in whole blood over time following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects.

[00284] A summary of plasma and whole blood pharmacokinetic parameters for total radioactivity following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects is presented in Table 12.

[00285] A summary (mean±SD) of the percentage of ^{14}C radioactivity associated with erythrocytes in whole blood (ETR) over time following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects is presented in Table 13.

[00286] Following a single oral dose, the peak radioactivity in plasma and whole blood were achieved at approximately 2 hours (median) with a mean maximum value (C_{max}) of 2000 and 1200 ngEq/mL, respectively. The elimination half-life ($t_{½}$) of the total radioactivity in plasma was determined with a mean value of 269 hours. However, the $t_{1/2}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}72}$ of the total radioactivity in whole blood were not reportable since $AUC_{0\text{-}t}$ / $AUC_{0\text{-}inf}$ ratio were less than 0.80 for those eight subjects. The mean values of systemic exposures ($AUC_{0\text{-}24}$ and $AUC_{0\text{-}72}$) in plasma were around 1.6 times higher than those in whole blood (Table 12).

[00287] Table 12. Summary (Mean ± SD and %CV) of Plasma and Whole Blood Pharmacokinetic Parameters for Total Radioactivity following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to Healthy Male Subjects.

Parameters	Plasma	Whole Blood	%Ratio of Plasma to Whole blood
C_{max}, ngEq/mL	2000±429 (21)	1200±243 (20)	167±12.4 (7)
t_{max}, h[a]	2.00 (1.00, 4.00)	2.00 (1.98, 2.00)	NA
$AUC_{0\text{-}t}$, h·ngEq/mL	259000±42700 (16)	54100±10300 (19)	487±73.3 (15)

AUC_{0-24}, h·ngEq/mL	31400±6380 (20)	19600±3780 (19)	160±6.65 (4)
AUC_{0-72}, h·ngEq/mL	89700±19000 (21)	54100±10300 (19)	165±11.1 (7)
AUC_{0-inf}, h·ngEq/mL	306000±59500 (19)	NR	NA
k_{el}, 1/h	0.00308±0.00182 (59)	NR	NA
$t_{½}$, h	269±93.2 (35)	NR	NA

[a]: median (range); NR: Not Reportable , since AUC_{0-t} / AUC_{0-inf} ratio < 0.80 ; NA: Not Applicable;
C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity.

[00288] The total radioactivity in whole blood and plasma was detectable in all subjects following single dosing. One of the purposes of this measurement was to characterize the partitioning of [^{14}C]-XL184 in erythrocytes and whole blood. Erythrocyte to whole blood concentration ratios were examined after single dosing. The details of calculation used to determine the erythrocyte-to-whole blood total radioactivity concentration ratios are described in Section 3.4.1.

[00289] The mean percent of total radioactivity concentrations associated with erythrocytes based on the concentration of total radioactive concentrations in plasma and whole blood ranged from 0.174 ± 4.51 to 12.3 ± 3.71 within 72 hours after single dosing, indicating that radioactivity was present primarily in plasma and not markedly associated with red blood cells (Table 13).

[00290] Table 13. Summary (Mean±SD and %CV) of Percentage of ^{14}C Radioactivity Associated with Erythrocytes in Whole Blood (ETR) over Time following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) containing 100 µCi [^{14}C]-XL184 to Healthy Male Subjects.

Time (hr)	Percentage (%)
1	7.08±5.93 (84)
2	7.85±3.27 (42)
4	6.40±2.05 (32)
8	12.2±5.00 (41)
14	12.3±3.71 (30)
24	0.174±4.51 (2595)
72	3.89±5.58 (143)

[00291] 4.2.2.2 Plasma Pharmacokinetic Parameters for XL184 and its metabolites by LC/MS/MS method

[00292] The individual and mean plasma concentration data for XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate by LC/MS/MS method after single dose administration of 175 mg of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 formulated as an oral solution in healthy male subjects are presented in Tables 28 to 32A. Para-fluoroaniline (pFA) metabolite concentrations were below the LLOQ for all subjects. The individual actual plasma sampling times are listed in Table 23. The individual subject and descriptive statistics plasma pharmacokinetic parameters of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate by LC/MS/MS method are included in Tables 33 to 36.

[00293] FIGS. 7 and 8 (linear axes) and FIGS. 9 and 10 (semi-logarithmic axes) illustrate the mean (±SD) plasma concentrations versus time plots of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate, respectively, measured by LC/MS/MS method after administration of single 175 mg dose of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 as an oral solution.

[00294] A summary of plasma pharmacokinetic parameters of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate measured by LC/MS/MS method following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects is presented in Table 14.

[00295] The parent compound, XL184, was rapidly absorbed after oral administration and eliminated relatively slowly. The main circulating metabolite in plasma was 6-Demethyl Half-Dimer Sulfate. Following a single oral dose, the mean peak concentrations of XL184, XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate in plasma were achieved at approximately 1.49, 18.99, 13.50, 24.00, and 168.00 hours (median) with a mean maximum concentration value (C_{max}) of 1250, 52.9, 118, 236 and 230 ng/mL, respectively. The mean estimated elimination half-lives of XL184, XL184-Half-Dimer, XL184-N-Oxide, and XL184-Sulfate were 102, 91.8, 89.2, and 86.0 hours, respectively (FIGS. 7, 8, 9, and 10 and Table 14). However, the elimination half-lives of 6-Demethyl Half-Dimer Sulfate for all the subjects could not be determined.

[00296] For metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate, the mean metabolite exposure ratios relative to parent XL184

(AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) were 9.93%, 15.0%, 42.9%, and 150%, respectively. Mean exposure ratios for parent and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate relative to total exposure, (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent+4 measured metabolites)) were 32.4%, 3.09%, 4.90%, 13.8%, and 45.9%, respectively.

[00297] Table 14. Summary (Mean ± SD and %CV) of Plasma Pharmacokinetic Parameters for XL184 and Selected Metabolites by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects.

Parameters	XL184	XL184-Half-Dimer	XL184-N-Oxide	XL184-Sulfate	6-Demethyl Half-Dimer Sulfate*
C_{max}, ng/mL	1250±238 (19)[e]	52.9±17.3 (33)	118±33.7 (28)	236±66.7 (28)	230±91.2 (40)
T_{max}, h[a]	1.49 (1.00, 3.00)	18.99 (5.00, 24.10)	13.50 (2.00, 24.30)	24.00 (3.00, 48.00)	168.00 (71.97, 240.00)
AUC_{0-24}, h·ng/mL	14300±2600 (18)	1080±341 (32)	2030±682 (34)	3970±1350 (34)	951±377 (40)
AUC_{0-72}, h·ng/mL	35000±6770 (19)	3120±976 (31)	5610±1940 (35)	12600±4180 (33)	7530±3200 (42)
AUC_{0-t}, h·ng/mL	67200±6880 (10)	6540±1680 (26)	10100±3210 (32)	28900±10700 (37)	99500±34500 (35)
Ratio[b], %	NA	9.93±3.20 (32)	15.0±3.80 (25)	42.9±14.4 (33)	150±51.5 (34)
Ratio[c], %	32.4±6.07 (19)	3.09±0.689 (22)	4.90±2.01 (41)	13.8±5.63 (41)	45.9±11.2 (24)
AUC_{0-inf}, h·ng/mL	68000±6910 (10)	6770±1700 (25)	10300±3170 (31)	29500±10600 (36)	NA
k_{el}, 1/h	0.00712±0.00176 (25)	0.00807±0.00218 (27)	0.00846±0.00256 (30)	0.00859±0.0022 (26)	NA
$t_{1/2}$, h	102±23.3 (23)	91.8±25.4 (28)	89.2±29.2 (33)	86.0±24.3 (28)	NA

[a]: median (range); [b]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [c]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent+4 measured metabolites); NA: Not Applicable; C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose;
AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; *: The LC/MS/MS analytical method for 6-demethy half-dimer sulfate is not validated.

[00298] 4.2.2.3 Plasma Pharmacokinetic Parameters for XL184 and its Metabolites using a Radio-Quantitation Method

[00299] Samples for 2 subjects were used for the investigation study. Therefore, only 6 subjects' PK profiles were determined using a radio-quantitation method. Due to the low radioactivity after 336 hours, the samples for 504 hours and 648 hours were not analyzed. The individual and mean plasma concentration data for XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, P2, and P7 using a radio-quantitative method after single dose administration of 175 mg of XL184 (L-

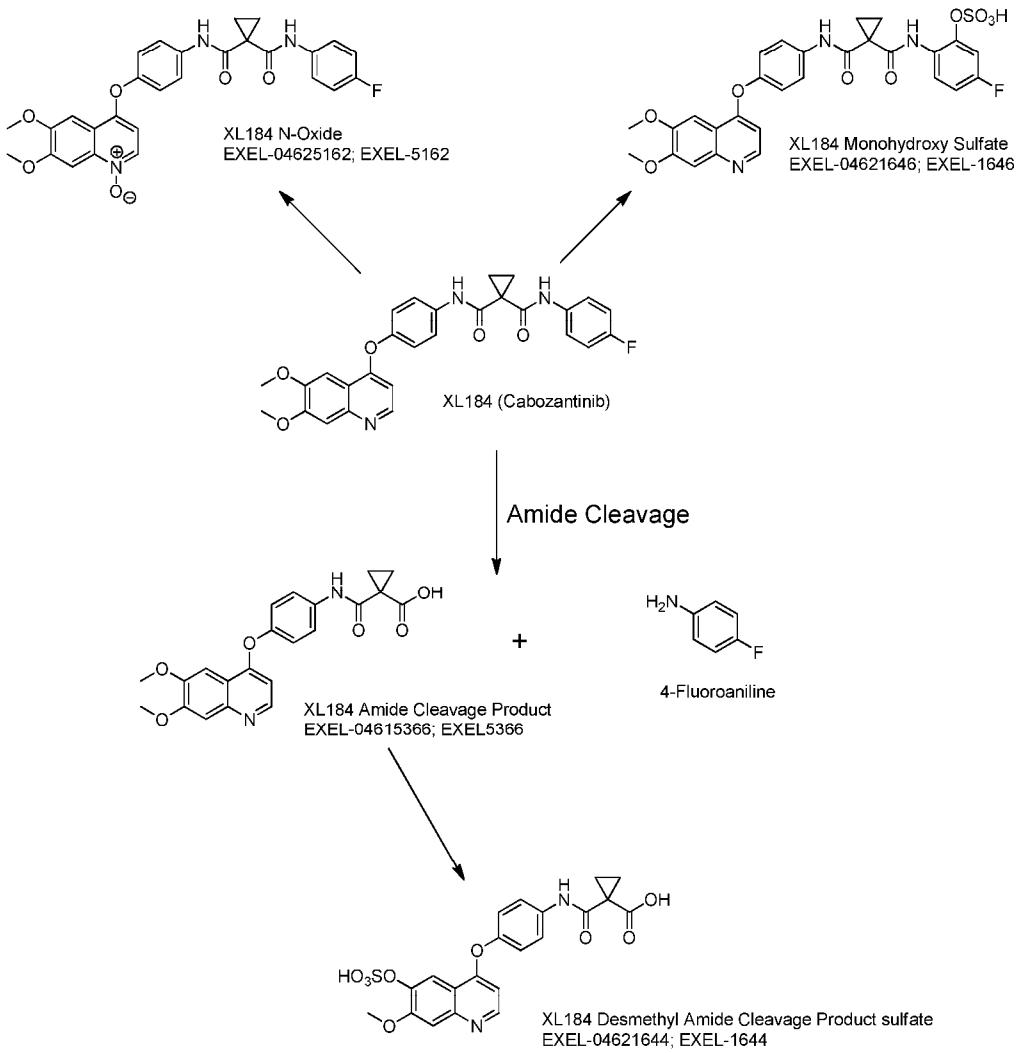
Malate Salt) containing 100 μCi [^{14}C]-XL184 formulated as an oral solution in healthy male subjects are presented in Table 15.

[00300] The individual actual plasma sampling times are listed in Table 23. The individual subject and descriptive statistics plasma pharmacokinetic parameters of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, P2, and P7 using a radio-quantitative method are included in Table 45. app

[00301] FIGS. 11 and 12 (linear axes) and FIGS. 13 and 14 (semi-logarithmic axes) illustrate the mean (±SD) plasma concentrations versus time plots of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7, respectively, measured by a radio-quantitative method after administration of single 175 mg dose of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 as an oral solution.

[00302] A summary of plasma pharmacokinetic parameters of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7, measured by a radio-quantitative method following a single 175 mg oral administration of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to healthy male subjects is presented in Table 15. Since no subjects had more than five consecutive data points with a quantifiable P2 concentration value, there is no pharmacokinetic parameter information included in Table 15. The proposed major biotransformation products of XL184 are displayed in Scheme 3.

Scheme 3.



[00303] The parent compound, XL184, was rapidly absorbed after oral administration and was eliminated relatively slowly. Following a single oral dose, the median peak concentrations of XL184, XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7 in plasma were achieved at approximately 1.99, 1.49, 3.00, 4.50, 71.99, 2.00, and 2.00 hours with a mean maximum concentration value (C_{max}) of 1080, 210, 299, 649, 379, 194, and 95.3 ngEq/mL, respectively. The mean estimated elimination half-lives of XL184, XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and P5 were 70.5, 57.9, 73.1, 79.2, and 73.4 hours, respectively (FIGS. 11, 12, 13, and 14 and Table 15). However, the elimination half-lives of 6-Demethyl Half-Dimer Sulfate and P7 for all the subjects were not reportable.

[00304] For metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7, the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) were 34.4%, 34.1%, 188%, 283%, 24.5%, and 1.54%, respectively. Mean exposure ratios for parent and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7 relative to total exposure (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + measured metabolites) were 20.0%, 6.25%, 7.16%, 37.6%, 40.3%, 4.10%, and 0.386%, respectively.

[00305] The results of the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) and the mean exposure ratios for parent and metabolites relative to total exposure (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + measured metabolites) between LC/MS/MS and the radio-quantitative method are different since they are two different methods. LC/MS/MS was a validated method (except for 6-Demethyl Half-Dimer Sulfate) and was run under the GLP environment in this study. On the contrary, the radio-quantitative method was not a validated method and was run under the non-GLP environment in this study.

[00306] **Table 15. Summary (Mean ± SD and %CV) of Plasma Pharmacokinetic Parameters for XL184 and Selected Metabolites Using a Radio-Quantitative Method* Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects (N=6).**

Parameters	XL184	XL184-Half-Dimer	XL184-N-Oxide	XL184-Sulfate	6-Demethyl Half-Dimer Sulfate	P5	P7
C_{max}, ngEq/mL	1080±234 (22)	210±73 (35)	299±56 (19)	649±132 (20)	379±151 (40)[g]	194±51.1 (26)[h]	95.3[i]
T_{max}, h[a]	1.99 (1.00, 4.00)	1.49 (1.00, 24.08)	3.00 (2.00, 4.00)	4.50 (1.98, 24.08)	71.99 (24.00, 168.00)[g]	2.00 (1.98, 5.00)[h]	2.00[i]
AUC_{0-24}, h·ngEq/mL	10700±3170 (30)	3610±1350 (37)	4300±1460 (34)	11300±2360 (21)	2520±1370 (54)[g]	2470±1290 (52)[h]	625[i]
AUC_{0-72}, h·ngEq/mL	23800±9340 (39)	8680±3980 (46)	10600±3490 (33)	33200±7940 (24)	17400±7000 (40)[g]	5950±2870 (48)[h]	625[i]
AUC_{0-t}, h·ngEq/mL	38100±12800 (34)	11100±5890 (53)	13300±8360 (63)	69900±22000 (31)	89000±32000 (36)[g]	7660±442 (6)[h]	510[i]
Ratio[b], %	NA	34.4±24.7 (72)	34.1±15.4 (45)	188±29.1 (15)	283±200 (71)	24.5±11.4 (47)	1.54[i]
Ratio[c], %	20.0±6.24 (31)	6.25±3.76 (60)	7.16±4.20 (59)	37.6±13.9 (37)	40.3±15.9 (40)	4.10±1.19 (29)	0.386[i]
AUC_{0-inf}, h·ngEq/mL	40300±12300 (30)	16400±1770 (11)[d]	20800±7640 (37)[e]	74500±22900 (31)	NA	8720[i]	NA
k_{el}, 1/h	0.0112±0.0053 (47)	0.0136±0.00672 (49)[d]	0.00976±0.00212 (22)[e]	0.00923±0.00221 (24)	NA	0.00945[i]	NA
$t_{1/2}$, h	70.5±23.2 (33)	57.9±28.4 (49)[d]	73.1±14.0 (19)[e]	79.2±21.4 (27)	NA	73.4[i]	NA

[a]: median (range); [b]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [c]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent+6 measured metabolites); NA: Not Applicable; [d]: N=2; [e]: N=3; NR: Not reportable. [g]: N=4; [h]:N=3; [i]: N=1; C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life. *: The radio-quantitative method was not performed according to GLP regulations.

[00307] 5. Conclusions

[00308] Following oral administration of the 175 mg dose of XL184 (L-Malate Salt) containing 100 μCi [^{14}C]-XL184 to eight male healthy volunteers, a mean recovery of total radioactivity of 81.09% was achieved within 48 days. Approximately 1% total mean radioactivity was recovered in feces and urine after Day 28 post-dose. The radioactivity was mainly eliminated in feces (53.79%) and the remainder in urine (27.29%).

[00309] Following a single oral dose, the peak radioactivity in plasma and whole blood was achieved at approximately 2 hours (median) with a mean maximum value (C_{max}) of 2000 and 1200 ngEq/mL, respectively. The elimination half-life of the total radioactivity in plasma was determined with a mean value of 269 hours. The mean values of systemic exposures (AUC_{0-24} and AUC_{0-72}) in plasma were around 1.6 times higher than those in whole blood.

[00310] The mean percent total radioactivity concentrations associated with erythrocytes relative to whole blood ranged from 0.174 ± 4.51 to 12.3 ± 3.71 within 72 hours after single dosing, indicating that radioactivity was present primarily in plasma and not markedly associated with red blood cells.

[00311] XL184 was rapidly absorbed after oral administration and eliminated relatively slowly. The main circulating metabolite in plasma was 6-Demethyl Half-Dimer Sulfate. Following a single oral dose, the mean peak concentrations of XL184 and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate in plasma by LC/MS/MS method were achieved at approximately 1.49, 18.99, 13.50, 24.00, and 168.00 hours (median) with a mean maximum concentration value (C_{max}) of 1250, 52.9, 118, 236, and 230 ng/mL, respectively. The mean estimated elimination half-lives of XL184, XL184-Half-Dimer, XL184-N-Oxide, and XL184-Sulfate were 102, 91.8, 89.2, and 86.0 hours, respectively. However, the elimination half-lives of 6-Demethyl Half-Dimer Sulfate for all the subjects could not be determined. Para-fluoroaniline (pFA) metabolite concentrations were below the LLOQ for all subjects.

[00312] For metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate, the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) by LC/MS/MS method were 9.93%, 15.0%, 42.9%, and 150%, respectively. Mean exposure ratios for parent and metabolites XL184-Half-

Dimer, XL184-N-Oxide, XL184-Sulfate, and 6-Demethyl Half-Dimer Sulfate relative to total exposure (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent+4 measured metabolites)) were 32.4%, 3.09%, 4.90%, 13.8%, and 45.9%, respectively.

[00313] Following a single oral dose, the median peak concentrations of XL184, XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7 in plasma using a radio-quantitative method were achieved at approximately 1.99, 1.49, 2.00, 4.50, 71.99, 2.00, and 2.00 hours with a mean maximum concentration value (C_{max}) of 1080, 210, 299, 649, 379, 194, and 95.3 ngEq/mL, respectively. The mean estimated elimination half-lives of XL184, XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, and P5 were 70.5, 57.9, 73.1, 79.2, and 73.4 hours, respectively

[00314] For metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7, the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) were 34.4%, 34.1%, 188%, 283%, 24.5%, and 1.54%, respectively. Mean exposure ratios for parent and metabolites XL184-Half-Dimer, XL184-N-Oxide, XL184-Sulfate, 6-Demethyl Half-Dimer Sulfate, P5, and P7 relative to total exposure (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + measured metabolites) were 20.0%, 6.25%, 7.16%, 37.6%, 40.3%, 4.10%, and 0.386%, respectively.

[00315] The results of the mean metabolite exposure ratios relative to parent XL184 (AUC_{0-t} (metabolite)/ AUC_{0-t} (parent)) and the mean exposure ratios for parent and metabolites relative to total exposure (AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + measured metabolites) between LC/MS/MS and the radio-quantitative method are different since they are two different methods. LC/MS/MS was a validated method (except for 6-Demethyl Half-Dimer Sulfate) and was run under the GLP environment in this study. On the contrary, the radio-quantitative method was not a validated method and was run under the non-GLP environment in this study.

[00316] Table 16. Individual Urine Cumulative Excretion of ^{14}C Total Radioactivity Following Administration of a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

		Subject								Summary Statistics		
Time Post-dose (Day)	Time Interval (hrs)	1444-1010	1444-1023	1444-1040	1444-1042	1444-1051	1444-1052	1444-1057	1444-1058	Mean	SD	CV%
0.33	8	0.75	1.29	1.08	2.31	1.56	1.08	1.38	1.24	1.34	0.46	34
1	24	2.32	4.30	3.22	7.81	3.81	3.89	4.78	3.38	4.19	1.64	39
2	48	4.70	8.75	6.39	14.86	7.68	8.34	9.68	7.07	8.43	3.01	36
3	72	7.26	13.09	9.22	20.34	11.00	12.23	13.67	9.75	12.07	3.96	33
4	96	9.65	16.19	11.53	24.39	13.47	15.11	16.57	12.11	14.88	4.52	30
5	120	11.74	18.60	13.44	27.04	15.59	17.46	18.91	13.86	17.08	4.77	28
6	144	13.48	20.51	14.81	28.88	16.94	19.11	20.68	15.33	18.72	4.90	26
7	168	15.03	22.11	15.82	30.27	18.00	20.49	22.01	16.62	20.04	4.95	25
8	192	16.27	23.34	16.60	31.32	19.36	21.56	23.11	18.17	21.22	4.91	23
9	216	17.35	24.24	17.22	32.02	20.33	22.44	23.99	19.02	22.08	4.86	22
10	240	18.26	25.17	17.67	32.59	21.12	23.24	24.71	19.68	22.81	4.85	21
11	264	19.07	25.95	18.05	32.99	21.78	24.03	25.27	20.23	23.42	4.82	21
12	288	19.85	26.61	18.34	33.28	22.27	24.73	25.73	20.71	23.94	4.77	20
13	312	20.51	27.11	18.55	33.54	22.61	25.24	26.07	21.05	24.34	4.75	20
14	336	21.13	27.58	18.73	33.74	23.12	25.70	26.34	21.33	24.71	4.72	19
15	360	21.69	27.98	18.88	33.91	23.45	26.14	26.60	21.59	25.03	4.70	19
16	384	22.15	28.33	18.98	34.05	23.85	26.49	26.82	21.79	25.31	4.69	19
17	408	22.54	28.64	19.08	34.16	24.21	26.80	26.99	21.96	25.55	4.67	18
18	432	22.89	28.85	19.16	34.24	24.52	27.05	27.13	22.12	25.75	4.65	18
19	456	23.22	29.10	19.23	34.32	24.81	27.28	27.25	22.24	25.93	4.65	18
20	480	23.48	29.30	19.29	34.38	25.04	27.46	27.34	22.34	26.08	4.64	18
23	504 - 552	24.15	29.80	19.40	34.51	25.59	27.94	27.56	22.57	26.44	4.64	18
26	576 - 624	24.69	30.14	19.49	34.62	25.98	28.27	27.71	22.74	26.71	4.63	17
29	648 - 696	25.11	30.38	19.55	34.68	26.26	28.49	27.81	22.85	26.89	4.63	17
32	720 - 768	25.36	30.54	19.59	34.73	26.46	28.64	27.88	22.93	27.02	4.63	17
35	792 - 840	25.52	30.67	19.61	34.77	26.61	28.77	27.94	22.99	27.11	4.64	17
38	864 - 912	25.56	30.76	19.63	34.81	26.72	28.86	27.98	23.04	27.17	4.65	17
41	936 - 984	25.56	30.84	19.65	34.83	26.80	28.92	28.02	23.07	27.21	4.66	17
44	1008 - 1056	25.56	30.90	19.78	34.85	26.86	28.98	28.04	23.11	27.26	4.64	17
47	1080 - 1128	25.56	30.95	19.78	34.88	26.91	29.02	28.07	23.13	27.29	4.65	17
48	1152	25.56	30.97	19.78	34.88	26.92	29.03	28.07	23.14	27.29	4.65	17

[00317] Table 17. Individual Feces Cumulative Excretion of ^{14}C Total Radioactivity Following Administration of a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

		Subject								Summary Statistics		
Time Post-dose (Day)	Time Interval (hrs)	1444-1010	1444-1023	1444-1040	1444-1042	1444-1051	1444-1052	1444-1057	1444-1058	Mean	SD	CV%
1	24.00	0.00	1.51	0.00	0.00	7.27	0.00	0.00	6.55	1.92	3.13	163
2	48.00	2.41	4.69	6.21	13.42	13.75	0.00	0.00	23.82	8.04	8.33	104
3	72.00	17.54	11.89	19.42	23.50	19.09	6.71	20.02	27.89	18.26	6.54	36
4	96.00	29.54	15.75	26.66	23.50	24.06	21.44	20.02	33.67	24.33	5.62	23
5	120.00	29.54	26.82	38.33	33.66	30.04	21.44	32.13	38.11	31.26	5.66	18
6	144.00	29.54	32.95	42.31	33.66	32.58	34.95	32.13	40.73	34.86	4.41	13
7	168.00	37.33	35.74	46.15	37.83	35.24	34.95	39.21	42.53	38.62	3.92	10
8	192.00	37.33	38.12	50.16	37.83	35.24	42.36	39.21	46.78	40.88	5.17	13
9	216.00	38.43	40.65	52.52	41.88	39.09	42.36	44.88	47.60	43.43	4.74	11
10	240.00	40.55	40.97	53.88	41.88	40.04	42.36	44.88	49.11	44.21	4.90	11
11	264.00	40.55	42.16	56.19	44.05	41.53	42.36	47.81	51.46	45.76	5.58	12
12	288.00	43.16	45.59	57.02	44.05	43.34	46.17	47.81	51.70	47.36	4.81	10
13	312.00	43.16	45.85	58.37	44.65	43.60	46.17	49.96	53.34	48.14	5.37	11
14	336.00	44.52	46.96	58.62	44.65	45.13	47.75	49.96	54.31	48.99	5.09	10
15	360.00	46.60	47.74	59.19	44.65	45.47	47.75	50.79	54.76	49.62	5.03	10
16	384.00	48.10	48.28	59.83	45.48	46.43	47.75	50.79	55.20	50.23	4.91	10
17	408.00	49.60	48.83	60.27	45.48	46.79	49.42	51.79	55.60	50.97	4.86	10
18	432.00	49.60	49.07	60.38	45.89	47.53	49.42	51.79	55.93	51.20	4.76	9
19	456.00	50.94	49.54	60.68	45.89	47.53	50.45	52.32	56.14	51.69	4.76	9
20	480.00	51.52	49.81	60.90	46.07	48.35	50.45	52.32	56.50	51.99	4.71	9
21	504.00	51.52	50.21	61.01	46.07	48.80	50.89	52.62	56.69	52.23	4.68	9
24	528 -576	52.49	50.91	61.34	46.17	49.60	51.46	52.95	57.04	52.75	4.64	9
27	600 - 648	52.58	51.55	61.60	46.35	49.90	51.79	53.09	57.29	53.02	4.63	9
30	672 -720	53.58	51.77	61.75	46.44	50.45	52.07	53.29	57.46	53.35	4.60	9
33	744 - 792	54.17	52.00	61.82	46.48	50.76	52.56	53.41	57.56	53.60	4.57	9
36	816 - 864	54.27	52.19	61.89	46.48	50.95	52.56	53.45	57.67	53.68	4.57	9
39	888 - 936	54.27	52.30	61.89	46.54	51.11	52.71	53.45	57.67	53.74	4.54	8
42	960 - 1008	54.27	52.41	61.89	46.54	51.22	52.81	53.45	57.67	53.78	4.52	8
45	1032 -1080	54.27	52.41	61.89	46.54	51.22	52.89	53.45	57.67	53.79	4.52	8
48	1104 -1152	54.27	52.41	61.89	46.54	51.22	52.89	53.45	57.67	53.79	4.52	8

[00318] Table 18. Individual and Mean (±SD) Total Cumulative Recoveries of XL184 Following Administration of a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

	%Dose Administered		
Subject	Urine	Feces	Total
1444-1010	25.56	54.27	79.83
1444-1023	30.97	52.41	83.38
1444-1040	19.78	61.89	81.67
1444-1042	34.88	46.54	81.42
1444-1051	26.92	51.22	78.14
1444-1052	29.03	52.89	81.92
1444-1057	28.07	53.45	81.52
1444-1058	23.14	57.67	80.81
N	8	8	8
Mean	27.29	53.79	81.09
SD	4.65	4.52	1.56
SE	1.65	1.60	0.55
Min	19.78	46.54	78.14
Median	27.50	53.17	81.47
Max	34.88	61.89	83.38
CV%	17	8	2
Geometric Mean	26.94	53.63	81.07

[00319] Table 19. Individual and Mean Plasma ^{14}C Total Radioactivity (ngEq/mL) Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.00	575.58	1170.98	1151.99	957.10	1166.03	828.28	562.37	625.13	1156.95
1444-1023	0.00	637.52	1307.24	1619.39	1679.68	1583.06	1398.91	1100.79	1072.71	1415.42
1444-1040	0.00	552.46	1494.70	2134.69	2072.76	2093.40	1824.19	1334.49	1493.87	1889.43
1444-1042	0.00	145.34	1165.20	2318.85	2358.48	2384.91	1938.98	1178.42	1366.70	2109.92
1444-1051	0.00	733.31	1703.63	1744.92	1535.99	1426.16	1209.80	926.55	949.67	1166.03
1444-1052	0.00	477.31	1296.51	2113.22	2389.04	1850.62	1538.47	1157.77	1204.02	1458.36
1444-1057	0.00	1003.35	2068.63	2189.20	1814.28	1859.70	1397.25	1177.59	1267.60	1455.06
1444-1058	0.00	677.98	1797.77	2277.56	1733.35	1788.68	1136.30	1383.22	1077.67	1461.67
N	8	8	8	8	8	8	8	8	8	8
Mean	0.00	600.36	1500.58	1943.73	1817.59	1769.07	1409.02	1102.65	1132.17	1514.11
SD	0.00	242.77	327.85	405.18	467.53	380.89	362.84	259.06	268.92	330.29
SEM	0.00	85.83	115.91	143.25	165.30	134.67	128.28	91.59	95.08	116.78
Min	0.00	145.34	1165.20	1151.99	957.10	1166.03	828.28	562.37	625.13	1156.95
Median	0.00	606.55	1400.97	2123.96	1773.82	1819.65	1398.08	1167.68	1140.85	1456.71
Max	0.00	1003.35	2068.63	2318.85	2389.04	2384.91	1938.98	1383.22	1493.87	2109.92
%CV	NA	40	22	21	26	22	26	23	24	22
GM	NA	537.97	1470.80	1899.92	1756.69	1731.81	1365.83	1068.66	1099.67	1484.70

GM: Geometric Mean; NA: not applicable; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity;

[00320] **Table 19A. Individual and Mean Plasma ^{14}C Total Radioactivity (ngEq/mL) Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	663.12	694.50	539.25	470.71	454.19	305.55	245.26	206.45	156.90	99.10
1444-1023	1130.52	861.31	610.27	561.54	516.95	317.93	202.32	165.16	125.52	94.14
1444-1040	1401.38	919.12	572.28	540.07	478.14	223.79	132.95	0.00	0.00	0.00
1444-1042	1689.59	1305.59	665.59	580.54	528.51	351.79	205.62	177.55	144.52	111.48
1444-1051	1131.35	913.33	618.52	537.60	535.94	371.61	248.57	206.45	146.99	130.48
1444-1052	1080.15	861.31	606.96	579.71	494.65	402.16	307.20	227.92	184.15	151.95
1444-1057	986.01	858.83	580.54	518.60	443.45	289.86	200.67	144.52	114.79	91.66
1444-1058	1392.30	1414.60	888.56	796.90	644.12	430.24	317.11	237.83	199.84	149.47
N	8	8	8	8	8	8	8	8	8	8
Mean	1184.30	978.57	635.25	573.21	511.99	336.62	232.46	170.74	134.09	103.54
SD	310.11	247.09	108.87	97.19	63.04	66.27	60.61	75.82	61.00	48.12
SEM	109.64	87.36	38.49	34.36	22.29	23.43	21.43	26.81	21.57	17.01
Min	663.12	694.50	539.25	470.71	443.45	223.79	132.95	0.00	0.00	0.00
Median	1130.94	887.32	608.62	550.81	505.80	334.86	225.44	192.00	145.76	105.29
Max	1689.59	1414.60	888.56	796.90	644.12	430.24	317.11	237.83	199.84	151.95
%CV	26	25	17	17	12	20	26	44	45	46
GM	1146.14	953.99	628.27	566.94	508.82	330.55	225.10	NA	NA	NA

GM: Geometric Mean; NA: not applicable; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity.

[00321] Table 20. Individual and Mean Whole Blood 14C Total Radioactivity (ngEq/mL) Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [14C]-XL184 (100 µCi) to Healthy Male Subjects

	Time (hours)							
Subject	0.00	1.00	2.00	4.00	8.00	14.00	24.00	72.00
1444-1010	0.00	717.47	763.98	742.45	395.34	432.38	701.11	452.19
1444-1023	0.00	839.78	998.26	928.49	647.70	695.94	764.84	503.00
1444-1040	0.00	916.43	1309.19	1303.16	873.37	908.68	986.20	540.04
1444-1042	0.00	776.04	1536.58	1458.20	813.08	941.41	1196.36	845.81
1444-1051	0.00	952.61	1077.50	879.40	620.14	624.45	692.49	562.44
1444-1052	0.00	817.38	1260.96	1162.77	799.30	744.17	883.70	510.76
1444-1057	0.00	1137.79	1222.20	1056.83	708.86	769.15	786.38	450.46
1444-1058	0.00	1136.07	1389.29	1048.21	821.69	720.05	854.42	764.84
N	8	8	8	8	8	8	8	8
Mean	0.00	911.70	1194.75	1072.44	709.94	729.53	858.19	578.69
SD	0.00	157.37	242.26	232.35	155.26	160.06	167.93	146.65
SEM	0.00	55.64	85.65	82.15	54.89	56.59	59.37	51.85
Min	0.00	717.47	763.98	742.45	395.34	432.38	692.49	450.46
Median	0.00	878.11	1241.58	1052.52	754.08	732.11	820.40	525.40
Max	0.00	1137.79	1536.58	1458.20	873.37	941.41	1196.36	845.81
%CV	NA	17	20	22	22	22	20	25
GM	NA	900.21	1171.16	1050.57	691.86	712.27	845.09	564.30

GM: Geometric Mean; NA: not applicable; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity

[00322] **Table 21. Individual and Mean Hematocrit Value**

Subject	Hematocrit (%)			
	Day -1	Day 2	Day 4	Mean
1444-1010	40.8	41.1	39.7	40.5
1444-1023	44.6	45.7	44.2	44.8
1444-1040	41.8	44.3	42.5	42.9
1444-1042	41.7	42.0	44.6	42.8
1444-1051	42.6	41.9	42.2	42.2
1444-1052	43.9	42.5	42.0	42.8
1444-1057	48.2	46.6	46.3	47.0
1444-1058	42.6	41.9	42.2	42.2
1444-1010	43.5	41.8	42.4	42.6

[00323] Table 22. Individual and Descriptive Statistics of the Percentage of ^{14}C Radioactivity Associated with Erythrocytes in Whole Blood (ETR) over Time Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 μCi) to Healthy Male Subjects

	Time (hours)						
Subject	1.00	2.00	4.00	8.00	14.00	24.00	72.00
1444-1010	2.89	10.3	6.55	15.4	14.0	1.81	8.62
1444-1023	14.1	10.5	5.88	6.19	14.9	-2.15	5.48
1444-1040	6.87	6.90	8.27	12.8	6.13	-9.40	2.82
1444-1042	14.1	13.7	6.45	17.1	17.0	-0.88	11.7
1444-1051	-3.37	6.40	6.26	13.6	12.1	2.68	6.14
1444-1052	9.27	4.14	8.96	17.2	7.45	5.60	3.54
1444-1057	3.64	5.07	6.74	12.0	12.7	1.93	-1.05
1444-1058	9.17	5.90	2.05	3.37	14.1	1.80	-6.16
N	8	8	8	8	8	8	8
Mean	7.08	7.85	6.40	12.2	12.3	0.174	3.89
SD	5.93	3.27	2.05	5.00	3.71	4.51	5.58
SEM	2.10	1.16	0.725	1.77	1.31	1.59	1.97
Min	-3.4	4.1	2.1	3.4	6.1	-9.4	-6.2
Median	8.0	6.7	6.5	13	13	1.8	4.5
Max	14	14	9.0	17	17	5.6	12
%CV	84	42	32	41	30	2595	143
GM	NA	7.30	5.96	10.9	11.7	NA	NA

ETR=Xe/Xb=1-[Cp×(1-Hct)/Cb], where Cp stands for concentration of radioactivity in plasma , Cb stands for concentration of radioactivity in blood and Hct stands for hemocrit value.

Hematocrit values for Days -1, 2, and 4 were averaged for use in this calculation. GM: geometric me

[00324] Table 23. Individual Subject Actual Blood Sampling Times for Plasma for Total Radioactivity and for Pharmacokinetic Analysis of XL184 and Its Metabolites Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 μCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.00	0.50	1.00	2.00	3.00	4.00	5.00	7.98	13.98	24.00
1444-1023	0.00	0.50	1.00	1.98	3.00	4.00	5.00	7.98	13.98	24.00
1444-1040	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.03
1444-1042	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	13.98	24.03
1444-1051	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	13.98	24.08
1444-1052	0.00	0.50	1.00	1.98	3.00	4.00	5.00	8.00	14.00	24.10
1444-1057	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.08
1444-1058	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	23.68

48-648 hrs

	Time (hours)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	48.03	72.00	120.00	144.00	168.00	240.00	336.00	407.98	504.00	648.00
1444-1023	48.00	72.00	120.00	144.00	168.00	239.98	336.00	407.98	504.00	648.00
1444-1040	48.00	72.00	120.00	143.98	168.00	240.00	336.00	408.00	503.98	648.00
1444-1042	48.00	71.97	120.00	143.98	168.00	240.00	336.00	407.98	503.98	648.00
1444-1051	48.00	71.98	120.00	144.00	167.98	240.00	336.00	407.98	503.98	647.98
1444-1052	48.00	71.98	120.00	143.98	168.00	240.00	335.87	407.98	503.98	648.00
1444-1057	48.00	71.98	120.00	144.00	168.00	240.00	335.95	407.98	503.98	647.98
1444-1058	48.00	72.00	119.98	143.98	168.00	240.00	336.00	407.98	503.98	648.00

[00325] **Table 24. Individual Subject Actual Blood Sampling Times for Whole Blood Analysis of Total Radioactivity Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)							
Subject	0.00	1.00	2.00	4.00	8.00	14.00	24.00	72.00
1444-1010	0.00	1.00	2.00	4.00	7.98	13.98	24.00	72.00
1444-1023	0.00	1.00	1.98	4.00	7.98	13.98	24.00	72.00
1444-1040	0.00	1.00	2.00	4.00	8.00	14.00	24.03	72.00
1444-1042	0.00	1.00	2.00	4.00	8.00	13.98	24.03	71.97
1444-1051	0.00	1.00	2.00	4.00	8.00	13.98	24.08	71.98
1444-1052	0.00	1.00	1.98	4.00	8.00	14.00	24.10	71.98
1444-1057	0.00	1.00	2.00	4.00	8.00	14.00	24.08	71.98
1444-1058	0.00	1.00	2.00	4.00	8.00	14.00	23.68	72.00

[00326] **Table 25. Individual Subject Actual Blood Sampling Times for Plasma for Possible Metabolic Profiling Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)														
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00	72.00	168.00	336.00	504.00	648.00
1444-1010	0.00	0.50	1.00	2.00	3.00	4.00	5.00	7.98	13.98	24.00	72.00	168.00	336.00	504.00	648.00
1444-1023	0.00	0.50	1.00	1.98	3.00	4.00	5.00	7.98	13.98	24.00	72.00	168.00	336.00	504.00	648.00
1444-1040	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.03	72.00	168.00	336.00	503.98	648.00
1444-1042	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	13.98	24.03	71.97	168.00	336.00	503.98	648.00
1444-1051	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	13.98	24.08	71.98	167.98	336.00	503.98	647.98
1444-1052	0.00	0.50	1.00	1.98	3.00	4.00	5.00	8.00	14.00	24.10	71.98	168.00	335.87	503.98	648.00
1444-1057	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.08	71.98	168.00	335.95	503.98	647.98
1444-1058	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	23.68	72.00	168.00	336.00	503.98	648.00

[00327] Table 26. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of Total Radioactivity Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject _ID	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1010	1170	1.00	216000	19400	57600	249000	0.00307	226
1444-1023	1680	3.00	244000	29600	84000	283000	0.00246	282
1444-1040	2130	2.00	210000	38700	106000	228000	0.00741	93.5
1444-1042	2380	4.00	302000	38700	120000	359000	0.00197	352
1444-1051	1740	2.00	258000	26400	78500	299000	0.00317	218
1444-1052	2390	3.00	278000	32800	86500	333000	0.00278	250
1444-1057	2190	2.00	234000	33400	84900	283000	0.00187	371
1444-1058	2280	2.00	333000	32000	99900	410000	0.00194	357
N	8	8	8	8	8	8	8	8
Mean	2000	2.38	259000	31400	89700	306000	0.00308	269
SD	429	0.92	42700	6380	19000	59500	0.00182	93.2
SEM	152	0.32	15100	2260	6720	21000	0.000644	33.0
Min	1170	1.00	210000	19400	57600	228000	0.00187	93.5
Median	2160	2.00	251000	32400	85700	291000	0.00262	266
Max	2390	4.00	333000	38700	120000	410000	0.00741	371
%CV	21	39	16	20	21	19	59	35
GM	1950	2.21	256000	30700	87900	301000	0.00278	250

GM: Geometric Mean; C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration;
AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity.

[00328] Table 27. Individual and Descriptive Statistics of Whole Blood Pharmacokinetic Parameters of Total Radioactivity following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	Ratio[c] (%)	Ratio[d] (%)
1444-1010	764	2.00	40700	13000	40700	153	531	149	142
1444-1023	998	1.98	48200	17800	48200	168	506	166	174
1444-1040	1310	2.00	60000	23400	60000	163	350	165	177
1444-1042	1540	2.00	74000	25000	74000	155	408	155	162
1444-1051	1080	2.00	46900	16800	46900	161	550	157	167
1444-1052	1260	1.98	54000	20600	54000	190	515	159	160
1444-1057	1220	2.00	49500	19800	49500	180	473	169	172
1444-1058	1390	2.00	59400	20500	59400	164	561	156	168
N	8	8	8	8	8	8	8	8	8
Mean	1200	2.00	54100	19600	54100	167	487	160	165
SD	243	0.01	10300	3780	10300	12.4	73.3	6.65	11.1
SEM	85.9	0.00	3650	1340	3660	4.39	25.9	2.35	3.92
Min	764	1.98	40700	13000	40700	153	350	149	142
Median	1240	2.00	51800	20100	51800	163	511	158	168
Max	1540	2.00	74000	25000	74000	190	561	169	177
%CV	20	0	19	19	19	7	15	4	7
GM	1170	1.99	53300	19300	53300	166	481	159	165

GM: Geometric Mean; AUC_{0-inf}, kel and t½ were not reportable since the value of AUC0-t / AUC_{0-inf} ratio for each subject was < 0.80; a, b, c and d: % ratio of plasma to whole blood for C_{max}, AUC0-t, $AUC_{0-24}$and AUC_{0-72}, respectively. C_{max}, maximum observed concentration; Tmax, time of the maximum concentration; AUC0-t, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC0-24, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC0-inf, area under the concentration-time curve from time zero to infinity; kel, apparent terminal elimination rate constant; t1/2, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; ngEq, an equivalent amount of XL184 freebase required to produce a measured or calculated amount of total radioactivity.

[00329] Table 28. Individual and Mean Plasma Concentrations (ng/mL) of XL184 by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.000	377.055	777.766	703.373	459.276	682.206	409.319	266.879	335.869	681.961
1444-1023	0.000	410.653	988.621	1026.742	1024.476	902.898	697.894	386.419	417.208	434.009
1444-1040	0.000	328.704	998.065	1441.786	1095.197	1063.173	970.873	687.933	487.884	860.448
1444-1042	0.000	59.305	914.945	1482.359	1310.794	1158.537	978.352	504.541	600.449	788.240
1444-1051	0.000	509.883	1240.897	953.447	793.118	732.686	547.741	382.217	366.964	435.770
1444-1052	0.000	350.200	841.426	1093.027	1319.899	1019.020	729.002	529.976	486.724	504.273
1444-1057	0.000	760.436	1403.846	1237.637	902.344	1025.043	700.088	531.908	523.762	547.776
1444-1058	0.000	488.450	1344.723	1241.830	889.579	844.899	513.445	700.302	397.419	534.139
N	8	8	8	8	8	8	8	8	8	8
Mean	0.000	410.586	1063.786	1147.525	974.335	928.558	693.339	498.772	452.035	598.327
SD	0.000	197.553	235.829	258.626	282.901	166.997	204.878	150.468	88.307	160.675
SEM	0.000	69.846	83.378	91.438	100.021	59.042	72.435	53.198	31.221	56.807
Min	0.000	59.305	777.766	703.373	459.276	682.206	409.319	266.879	335.869	434.009
Median	0.000	393.854	993.343	1165.332	963.410	960.959	698.991	517.259	451.966	540.958
Max	0.000	760.436	1403.846	1482.359	1319.899	1158.537	978.352	700.302	600.449	860.448
%CV	NA	48	22	23	29	18	30	30	20	27
GM	NA	344.890	1041.459	1119.787	931.654	914.828	666.511	477.461	444.581	580.567

NA: Not Applicable; GM: Geometric Mean

[00330] Table 28A. Individual and Mean Plasma Concentrations (ng/mL) of XL184 by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

48-648 hrs

	Time (hours)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	283.853	254.530	156.488	122.688	163.095	90.153	65.102	43.328	27.834	10.464
1444-1023	333.638	255.041	147.087	145.915	135.606	49.766	35.903	21.636	13.009	6.311
1444-1040	489.217	246.732	179.421	172.821	134.168	55.790	24.788	10.908	5.771	2.424
1444-1042	614.498	411.177	148.076	107.202	75.695	39.898	10.711	4.879	1.968	0.000
1444-1051	424.868	305.315	154.063	125.163	121.433	71.462	39.049	25.305	14.396	8.189
1444-1052	352.213	255.189	118.584	114.427	97.118	65.257	38.068	17.412	11.462	3.790
1444-1057	307.958	244.280	113.195	116.918	92.425	44.384	19.250	10.002	3.954	2.050
1444-1058	516.059	418.464	184.363	162.622	115.395	61.247	24.467	10.756	6.704	2.270
N	8	8	8	8	8	8	8	8	8	8
Mean	415.288	298.841	150.160	133.470	116.867	59.745	32.167	18.028	10.637	4.437
SD	116.396	74.114	25.238	24.098	28.013	16.211	16.569	12.232	8.239	3.555
SEM	41.152	26.203	8.923	8.520	9.904	5.732	5.858	4.325	2.913	1.257
Min	283.853	244.280	113.195	107.202	75.695	39.898	10.711	4.879	1.968	0.000
Median	388.541	255.115	151.070	123.926	118.414	58.519	30.346	14.160	9.083	3.107
Max	614.498	418.464	184.363	172.821	163.095	90.153	65.102	43.328	27.834	10.464
%CV	28	25	17	18	24	27	52	68	77	80
GM	401.634	291.722	148.236	131.665	113.863	57.917	28.494	14.850	8.070	NA

NA: Not Applicable; GM: Geometric Mean

[00331] Table 29. Individual and Mean Plasma Concentrations (ng/mL) of XL184 Half-Dimer by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.000	4.846	13.450	23.314	24.221	27.171	24.260	22.875	31.511	35.627
1444-1023	0.000	4.593	17.564	31.523	33.843	34.651	35.617	38.445	37.909	37.924
1444-1040	0.000	4.531	14.478	27.120	29.439	32.345	32.584	28.090	34.054	35.050
1444-1042	0.000	0.000	17.132	43.143	52.416	54.336	76.749	63.237	68.777	75.680
1444-1051	0.000	4.356	17.489	28.961	31.495	36.085	36.373	38.175	40.841	35.055
1444-1052	0.000	4.261	21.194	35.430	44.061	49.890	55.705	63.530	65.263	67.985
1444-1057	0.000	8.367	24.937	37.927	38.602	51.831	50.493	57.434	69.700	69.776
1444-1058	0.000	6.794	23.881	35.764	38.359	42.571	43.260	58.592	47.769	56.247
N	8	8	8	8	8	8	8	8	8	8
Mean	0.000	4.719	18.766	32.898	36.555	41.110	44.380	46.297	49.478	51.668
SD	0.000	2.399	4.184	6.409	8.873	10.051	16.473	16.331	16.047	17.688
SEM	0.000	0.848	1.479	2.266	3.137	3.554	5.824	5.774	5.674	6.254
Min	0.000	0.000	13.450	23.314	24.221	27.171	24.260	22.875	31.511	35.050
Median	0.000	4.562	17.527	33.477	36.101	39.328	39.817	47.940	44.305	47.086
Max	0.000	8.367	24.937	43.143	52.416	54.336	76.749	63.530	69.700	75.680
%CV	NA	51	22	19	24	24	37	35	32	34
GM	NA	NA	18.364	32.341	35.633	40.015	41.935	43.470	47.247	49.053

NA: Not Applicable; GM: Geometric Mean

[00332] Table 29A. Individual and Mean Plasma Concentrations (ng/mL) of XL184 Half-Dimer by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

48-648 hrs

	Time (hours)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	30.648	24.554	18.190	14.057	11.729	7.495	5.228	2.998	2.084	0.000
1444-1023	36.546	24.587	16.438	15.153	12.065	5.903	2.034	1.806	1.083	0.000
1444-1040	26.242	19.464	11.095	9.729	8.353	2.927	1.209	0.000	0.000	0.000
1444-1042	56.997	42.700	17.753	13.747	9.922	4.398	1.547	0.000	0.000	0.000
1444-1051	33.055	23.197	13.375	11.927	12.076	7.066	3.887	2.509	1.813	0.000
1444-1052	56.829	46.257	21.732	19.455	16.224	8.332	5.513	2.769	1.445	0.000
1444-1057	53.673	44.053	23.839	20.401	17.365	7.257	3.352	2.045	0.000	0.000
1444-1058	48.913	35.430	25.809	23.143	16.260	8.677	3.578	1.740	0.000	0.000
N	8	8	8	8	8	8	8	8	8	8
Mean	42.863	32.530	18.529	15.952	12.999	6.507	3.294	1.733	0.803	0.000
SD	12.592	10.807	5.048	4.595	3.262	1.983	1.607	1.158	0.905	0.000
SEM	4.452	3.821	1.785	1.625	1.153	0.701	0.568	0.409	0.320	0.000
Min	26.242	19.464	11.095	9.729	8.353	2.927	1.209	0.000	0.000	0.000
Median	42.730	30.009	17.972	14.605	12.071	7.162	3.465	1.926	0.542	0.000
Max	56.997	46.257	25.809	23.143	17.365	8.677	5.513	2.998	2.084	0.000
%CV	29	33	27	29	25	30	49	67	113	NA
GM	41.175	30.943	17.899	15.374	12.633	6.174	2.908	NA	NA	NA

NA: Not Applicable; GM: Geometric Mean

[00333] Table 30. Individual and Mean Plasma Concentrations (ng/mL) of XL184-N-Oxide by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.000	11.529	42.306	49.777	46.221	57.466	38.445	33.122	25.454	64.769
1444-1023	0.000	15.944	47.387	65.128	82.005	78.375	78.220	67.430	63.633	101.490
1444-1040	0.000	17.041	82.525	149.634	167.092	150.220	135.223	125.712	140.835	178.702
1444-1042	0.000	1.789	40.311	104.019	108.484	115.106	103.517	66.642	73.090	129.577
1444-1051	0.000	13.441	67.257	94.858	92.250	91.248	79.258	68.805	66.930	84.372
1444-1052	0.000	14.585	67.753	103.201	134.615	124.375	89.247	85.963	71.593	84.326
1444-1057	0.000	27.247	92.619	113.541	90.538	111.017	86.573	79.003	80.870	93.700
1444-1058	0.000	20.854	97.364	128.577	118.153	125.842	88.903	115.660	68.937	113.468
N	8	8	8	8	8	8	8	8	8	8
Mean	0.000	15.304	67.190	101.092	104.920	106.706	87.423	80.292	73.918	106.301
SD	0.000	7.346	22.445	32.172	36.397	29.586	26.993	29.414	31.759	35.266
SEM	0.000	2.597	7.935	11.375	12.868	10.460	9.543	10.400	11.229	12.468
Min	0.000	1.789	40.311	49.777	46.221	57.466	38.445	33.122	25.454	64.769
Median	0.000	15.265	67.505	103.610	100.367	113.062	87.738	73.904	70.265	97.595
Max	0.000	27.247	97.364	149.634	167.092	150.220	135.223	125.712	140.835	178.702
%CV	NA	48	33	32	35	28	31	37	43	33
GM	NA	12.572	63.787	95.996	98.865	102.671	83.180	75.094	67.779	101.778

NA: Not Applicable; GM: Geometric Mean

[00334] Table 30A. Individual and Mean Plasma Concentrations (ng/mL) of XL184-N-Oxide by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

48-648 hrs

	Time (hours)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	29.036	28.612	21.842	13.355	13.351	7.415	4.583	3.326	1.817	1.062
1444-1023	64.132	40.828	19.980	19.507	14.871	5.771	2.530	1.964	0.000	0.000
1444-1040	116.958	82.612	51.850	35.583	26.090	10.327	4.459	1.674	1.094	0.000
1444-1042	90.059	63.663	20.037	13.485	10.109	4.830	1.199	0.000	0.000	0.000
1444-1051	69.537	47.911	25.291	19.696	18.011	9.570	5.079	3.200	2.005	0.000
1444-1052	50.889	33.767	16.002	11.804	9.229	6.267	2.973	1.678	1.052	0.000
1444-1057	49.764	40.895	21.335	17.057	14.433	5.546	2.390	1.382	0.000	0.000
1444-1058	89.002	76.099	31.817	30.113	19.166	9.684	4.176	1.946	1.237	0.000
N	8	8	8	8	8	8	8	8	8	8
Mean	69.922	51.798	26.019	20.075	15.658	7.426	3.424	1.896	0.901	0.133
SD	27.918	19.992	11.423	8.517	5.428	2.154	1.349	1.049	0.816	0.375
SEM	9.870	7.068	4.039	3.011	1.919	0.761	0.477	0.371	0.289	0.133
Min	29.036	28.612	16.002	11.804	9.229	4.830	1.199	0.000	0.000	0.000
Median	66.835	44.403	21.589	18.282	14.652	6.841	3.575	1.812	1.073	0.000
Max	116.958	82.612	51.850	35.583	26.090	10.327	5.079	3.326	2.005	1.062
%CV	40	39	44	42	35	29	39	55	91	283
GM	64.709	48.563	24.374	18.696	14.883	7.156	3.136	NA	NA	NA

NA: Not Applicable; GM: Geometric Mean

[00335] Table 31. Individual and Mean Plasma Concentrations (ng/mL) of XL184-Sulfate by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.000	26.136	53.208	75.013	69.493	92.232	65.650	37.746	34.395	112.189
1444-1023	0.000	39.062	88.742	138.826	158.824	179.491	172.724	130.798	131.091	233.292
1444-1040	0.000	45.896	145.829	249.626	310.748	267.057	283.604	197.270	268.052	306.497
1444-1042	0.000	6.360	78.291	157.511	203.331	205.443	243.196	98.885	127.544	287.276
1444-1051	0.000	29.730	96.816	126.368	141.682	148.181	125.679	108.976	133.704	174.720
1444-1052	0.000	32.267	120.212	157.200	194.021	215.476	174.760	143.215	153.538	205.532
1444-1057	0.000	59.658	156.410	180.378	187.282	226.697	174.947	159.230	198.553	262.691
1444-1058	0.000	43.796	143.662	181.953	231.546	216.139	162.694	204.329	153.379	289.913
N	8	8	8	8	8	8	8	8	8	8
Mean	0.000	35.363	110.396	158.359	187.116	193.840	175.407	135.056	150.032	234.014
SD	0.000	15.828	36.898	50.320	69.969	53.659	66.538	54.506	66.343	66.769
SEM	0.000	5.596	13.045	17.791	24.738	18.971	23.525	19.271	23.456	23.606
Min	0.000	6.360	53.208	75.013	69.493	92.232	65.650	37.746	34.395	112.189
Median	0.000	35.665	108.514	157.356	190.652	210.460	173.742	137.007	143.542	247.992
Max	0.000	59.658	156.410	249.626	310.748	267.057	283.604	204.329	268.052	306.497
%CV	NA	45	33	32	37	28	38	40	44	29
GM	NA	30.490	104.387	150.767	173.768	185.812	162.613	121.946	132.738	223.841

NA: Not Applicable; GM: Geometric Mean

[00337] Table 31A. Individual and Mean Plasma Concentrations (ng/mL) of XL184-Sulfate by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

48-648 hrs

	Time (hrs)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	45.563	50.547	46.211	27.744	23.691	11.649	8.367	5.228	0.000	0.000
1444-1023	146.630	132.711	90.680	85.890	73.594	26.053	9.824	5.311	0.000	0.000
1444-1040	230.932	198.580	156.507	125.712	112.019	47.012	18.863	9.010	4.723	0.000
1444-1042	220.082	185.825	81.561	61.841	46.492	21.297	5.717	0.000	0.000	0.000
1444-1051	176.870	152.441	95.518	73.454	73.048	36.170	20.502	13.626	7.874	4.167
1444-1052	130.352	106.815	47.419	37.916	27.883	16.190	10.596	4.971	0.000	0.000
1444-1057	147.459	151.276	89.982	80.113	61.829	30.106	11.580	6.347	0.000	0.000
1444-1058	258.933	211.280	149.901	151.619	97.444	49.589	22.349	8.128	4.996	0.000
N	8	8	8	8	8	8	8	8	8	8
Mean	169.603	148.684	94.722	80.536	64.500	29.758	13.475	6.578	2.199	0.521
SD	67.915	52.708	40.823	41.620	31.252	13.782	6.195	3.916	3.175	1.473
SEM	24.011	18.635	14.433	14.715	11.049	4.873	2.190	1.384	1.123	0.521
Min	45.563	50.547	46.211	27.744	23.691	11.649	5.717	0.000	0.000	0.000
Median	162.165	151.859	90.331	76.784	67.439	28.080	11.088	5.829	0.000	0.000
Max	258.933	211.280	156.507	151.619	112.019	49.589	22.349	13.626	7.874	4.167
%CV	40	35	43	52	48	46	46	60	144	283
GM	152.912	137.642	86.953	70.735	57.000	26.794	12.223	NA	NA	NA

NA: Not Applicable; GM: Geometric Mean

[00338] Table 32. Individual and Mean Plasma Concentrations (ng/mL) of 6-Demethyl Half-Dimer Sulfate by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

0-24 hrs

	Time (hours)									
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00
1444-1010	0.000	0.000	0.000	0.000	3.386	5.641	8.608	15.507	34.150	51.405
1444-1023	0.000	0.000	0.000	2.592	6.599	11.121	15.479	32.187	47.455	99.900
1444-1040	0.000	0.000	0.000	0.000	2.692	3.416	6.003	10.485	18.220	27.408
1444-1042	0.000	0.000	0.000	2.376	6.406	11.906	19.210	40.794	76.906	141.432
1444-1051	0.000	0.000	0.000	2.132	5.610	8.166	12.887	24.346	50.905	71.492
1444-1052	0.000	0.000	0.000	0.000	3.763	6.466	10.265	23.612	54.607	79.917
1444-1057	0.000	0.000	0.000	0.000	3.139	5.576	8.199	17.826	44.580	71.085
1444-1058	0.000	0.000	0.000	2.672	6.542	10.442	16.258	31.365	69.308	107.045
N	8	8	8	8	8	8	8	8	8	8
Mean	0.000	0.000	0.000	1.222	4.767	7.842	12.114	24.515	49.516	81.211
SD	0.000	0.000	0.000	1.315	1.681	3.061	4.595	9.960	18.570	35.102
SEM	0.000	0.000	0.000	0.465	0.594	1.082	1.625	3.521	6.566	12.410
Min	0.000	0.000	0.000	0.000	2.692	3.416	6.003	10.485	18.220	27.408
Median	0.000	0.000	0.000	1.066	4.687	7.316	11.576	23.979	49.180	75.705
Max	0.000	0.000	0.000	2.672	6.599	11.906	19.210	40.794	76.906	141.432
%CV	NA	NA	NA	108	35	39	38	41	38	43
GM	NA	NA	NA	NA	4.496	7.275	11.327	22.623	45.842	73.647

NA: Not Applicable; GM: Geometric Mean

[00339] Table 32A. Individual and Mean Plasma Concentrations (ng/mL) of 6-Demethyl Half-Dimer Sulfate by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 μCi) to Healthy Male Subjects

48-648 hrs

	Time (hrs)									
Subject	48.00	72.00	120.00	144.00	168.00	240.00	336.00	408.00	504.00	648.00
1444-1010	84.732	122.418	164.550	168.502	174.221	159.028	158.082	144.822	127.233	97.753
1444-1023	141.710	176.888	212.151	207.554	215.785	198.217	177.675	135.964	125.529	108.334
1444-1040	49.742	59.747	72.988	67.894	85.113	66.807	59.122	46.038	39.328	29.436
1444-1042	223.640	323.165	247.344	250.230	267.533	212.848	186.228	150.688	141.540	107.324
1444-1051	146.757	146.869	154.952	157.981	173.296	176.893	133.908	136.789	121.149	105.230
1444-1052	149.399	208.455	242.883	243.269	274.906	245.792	222.108	179.242	162.042	157.284
1444-1057	117.309	162.565	179.245	188.012	215.041	170.955	150.313	120.915	121.615	104.173
1444-1058	218.918	271.897	311.399	288.310	371.830	297.836	225.057	208.293	202.228	143.171
N	8	8	8	8	8	8	8	8	8	8
Mean	141.526	184.001	198.189	196.469	222.216	191.047	164.062	140.344	130.083	106.588
SD	59.831	83.504	72.171	68.143	85.190	67.604	53.336	47.147	45.942	37.702
SEM	21.153	29.523	25.516	24.092	30.119	23.902	18.857	16.669	16.243	13.330
Min	49.742	59.747	72.988	67.894	85.113	66.807	59.122	46.038	39.328	29.436
Median	144.234	169.727	195.698	197.783	215.413	187.555	167.879	140.806	126.381	106.277
Max	223.640	323.165	311.399	288.310	371.830	297.836	225.057	208.293	202.228	157.284
%CV	42	45	36	35	38	35	33	34	35	35
GM	128.687	165.608	184.175	182.634	206.142	177.656	153.681	130.546	119.974	97.637

NA: Not Applicable; GM: Geometric Mean

[00340] Table 33. Individual and Descriptive Statistics of XL184 Plasma Pharmacokinetic Parameters by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (h·ng/mL)	AUC_{0-72} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	AUC_{0-inf} (h·ng/mL)	k_{el} (1/h)	$t_{½}$ (h)	Ratio[a] (%)
1444-1010	778	1.00	10700	28800	72100	73900	0.0058	119	39.5
1444-1023	1030	1.98	12500	28800	61300	62500	0.00512	135	30.2
1444-1040	1440	2.00	17800	42800	74300	74700	0.00625	111	43.3
1444-1042	1480	2.00	17600	46800	72900	73100	0.0101	69.0	30.7
1444-1051	1240	1.00	11600	30700	66100	67500	0.00575	121	33.0
1444-1052	1320	3.00	14500	32100	61700	62200	0.00675	103	27.6
1444-1057	1400	1.00	15300	32200	56200	56400	0.00862	80.4	29.2
1444-1058	1340	1.00	14300	38100	73300	73500	0.00856	81.0	25.6
N	8	8	8	8	8	8	8	8	8
Mean	1250	1.62	14300	35000	67200	68000	0.00712	102	32.4
SD	238	0.74	2600	6770	6880	6910	0.00176	23.3	6.07
SEM	84.1	0.26	919	2390	2430	2440	0.000623	8.25	2.15
Min	778	1.00	10700	28800	56200	56400	0.00512	69.0	25.6
Median	1330	1.49	14400	32100	69100	70300	0.0065	107	30.4
Max	1480	3.00	17800	46800	74300	74700	0.0101	135	43.3
%CV	19	46	18	19	10	10	25	23	19
GM	1230	1.49	14100	34500	66900	67700	0.00694	100	31.9

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 4 measured metabolites);
C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; kel, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution.

[00341] Table 33A. Individual and Descriptive Statistics of XL184-Half-Dimer Plasma Pharmacokinetic Parameters by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (h·ng/mL)	AUC_{0-72} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ng/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1010	35.6	24.00	669	2130	5690	7.89	3.11	6080	0.00531	131
1444-1023	38.4	7.98	853	2480	5470	8.92	2.69	5610	0.00786	88.2
1444-1040	35.1	24.03	741	2030	3830	5.15	2.23	3940	0.0108	64.2
1444-1042	76.7	5.00	1530	4320	7230	9.92	3.05	7370	0.0111	62.7
1444-1051	40.8	13.98	859	2350	5470	8.28	2.73	5800	0.00557	124
1444-1052	68.0	24.10	1410	4140	8740	14.2	3.90	8950	0.00708	97.9
1444-1057	69.8	24.08	1420	4070	8270	14.7	4.30	8550	0.00757	91.6
1444-1058	58.6	8.00	1150	3430	7630	10.4	2.66	7820	0.0093	74.5
N	8	8	8	8	8	8	8	8	8	8
Mean	52.9	16.40	1080	3120	6540	9.93	3.09	6770	0.00807	91.8
SD	17.3	8.55	341	976	1680	3.20	0.689	1700	0.00218	25.4
SEM	6.10	3.02	120	345	595	1.13	0.244	600	0.000771	9.00
Min	35.1	5.00	669	2030	3830	5.15	2.23	3940	0.00531	62.7
Median	49.7	18.99	1010	2950	6460	9.42	2.89	6730	0.00772	89.9
Max	76.7	24.10	1530	4320	8740	14.7	4.30	8950	0.0111	131
%CV	33	52	32	31	26	32	22	25	27	28
GM	50.4	14.02	1030	2980	6340	9.47	3.02	6560	0.00781	88.8

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 4 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution.

[00342] Table 34. Individual and Descriptive Statistics of XL184-N-Oxide Plasma Pharmacokinetic Parameters by LC/MS/MS Method Following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (h·ng/mL)	AUC_{0-72} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ng/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1010	64.8	24.00	945	2760	6780	9.40	3.71	7000	0.00486	143
1444-1023	101	24.00	1750	4990	8640	14.1	4.25	8850	0.00928	74.7
1444-1040	179	24.03	3390	9340	16700	22.5	9.74	16800	0.0109	63.5
1444-1042	130	24.03	2100	6580	10100	13.9	4.26	10200	0.0126	54.8
1444-1051	94.9	2.00	1760	5020	10000	15.1	4.99	10300	0.00596	116
1444-1052	135	3.00	1980	4620	7700	12.5	3.44	7850	0.00684	101
1444-1057	114	2.00	2040	4850	8420	15.0	4.37	8590	0.0083	83.5
1444-1058	129	2.00	2280	6690	12700	17.3	4.44	12800	0.00895	77.4
N	8	8	8	8	8	8	8	8	8	8
Mean	118	13.13	2030	5610	10100	15.0	4.90	10300	0.00846	89.2
SD	33.7	11.64	682	1940	3210	3.80	2.01	3170	0.00256	29.2
SEM	11.9	4.11	241	686	1130	1.34	0.711	1120	0.000905	10.3
Min	64.8	2.00	945	2760	6780	9.40	3.44	7000	0.00486	54.8
Median	122	13.50	2010	5010	9320	14.5	4.31	9530	0.00863	80.5
Max	179	24.03	3390	9340	16700	22.5	9.74	16800	0.0126	143
%CV	28	89	34	35	32	25	41	31	30	33
GM	114	7.29	1930	5320	9750	14.6	4.65	9930	0.00811	85.3

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 4 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution.

[00343] Table 35. Individual and Descriptive Statistics of XL184-Sulfate Plasma Pharmacokinetic Parameters by LC/MS/MS Method following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (h·ng/mL)	AUC_{0-72} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ng/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1010	112	24.00	1430	4470	11000	15.3	6.02	11900	0.00619	112
1444-1023	233	24.00	3710	11600	26900	43.9	13.2	27400	0.0095	72.9
1444-1040	311	3.00	6090	17700	43000	57.9	25.1	43500	0.00948	73.1
1444-1042	287	24.03	4020	15000	28100	38.5	11.8	28600	0.0122	56.8
1444-1051	177	48.00	3190	11400	30900	46.7	15.4	31700	0.00532	130
1444-1052	215	4.00	3920	10800	19700	31.9	8.80	20400	0.00734	94.4
1444-1057	263	24.08	4710	13200	28700	51.1	14.9	29400	0.00953	72.8
1444-1058	290	23.68	4700	16900	42700	58.3	14.9	43200	0.00913	75.9
N	8	8	8	8	8	8	8	8	8	8
Mean	236	21.85	3970	12600	28900	42.9	13.8	29500	0.00859	86.0
SD	66.7	14.04	1350	4180	10700	14.4	5.63	10600	0.00220	24.3
SEM	23.6	4.96	477	1480	3790	5.08	1.99	3750	0.000777	8.61
Min	112	3.00	1430	4470	11000	15.3	6.02	11900	0.00532	56.8
Median	248	24.00	3970	12400	28400	45.3	14.1	29000	0.00931	74.5
Max	311	48.00	6090	17700	43000	58.3	25.1	43500	0.0122	130
%CV	28	64	34	33	37	33	41	36	26	28
GM	226	16.11	3710	11800	26800	40.1	12.8	27600	0.00833	83.2

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 4 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution.

[00344] **Table 36. Individual and Descriptive Statistics of 6-Demethyl Half-Dimer Sulfate Plasma Pharmacokinetic Parameters by LC/MS/MS Method following a Single 175 mg Oral Administration of XL184 (L-Malate Salt) Containing [^{14}C]-XL184 (100 μCi) to Healthy Male Subjects**

Subject	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24} (h·ng/mL)	AUC_{0-72} (h·ng/mL)	AUC_{0-t} (h·ng/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ng/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1010	174	168.00	627	4750	87100	121	47.7	NR	NR	NR
1444-1023	216	168.00	1080	7800	101000	165	49.7	NR	NR	NR
1444-1040	85.1	168.00	348	2590	33600	45.2	19.6	NR	NR	NR
1444-1042	323	71.97	1570	12500	119000	163	50.1	NR	NR	NR
1444-1051	177	240.00	916	7060	88000	133	43.9	NR	NR	NR
1444-1052	275	168.00	972	8020	126000	204	56.3	NR	NR	NR
1444-1057	215	168.00	816	6430	90900	162	47.2	NR	NR	NR
1444-1058	372	168.00	1290	11100	150000	205	52.4	NR	NR	NR
N	8	8	8	8	8	8	8	NA	NA	NA
Mean	230	165.00	951	7530	99500	150	45.9	NA	NA	NA
SD	91.2	45.25	377	3200	34500	51.5	11.2	NA	NA	NA
SEM	32.2	16.00	133	1130	12200	18.2	3.97	NA	NA	NA
Min	85.1	71.97	348	2590	33600	45.2	19.6	NA	NA	NA
Median	216	168.00	944	7430	96000	162	48.7	NA	NA	NA
Max	372	240.00	1570	12500	150000	205	56.3	NA	NA	NA
%CV	40	27	40	42	35	34	24	NA	NA	NA
GM	212	158.00	875	6850	92400	138	44.1	NA	NA	NA

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 4 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; NA: Not applicable; NR: Not reportable.

[00345] Table 37. Individual and Mean Plasma Concentrations (ngEq/mL) of XL184 using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

[00346]

	Time (hours)												
Subject	0.00	0.50	1.00	2.00	3.00	4.00	5.00	8.00	14.00	24.00	72.00	168.00	336.00
1444-1023	0.0	325.6	706.6	894.9	752.7	675.6	511.9	349.8	251.3	254.6	101.4	51.2	10.3
1444-1040	0.0	282.6	820.7	1132.9	876.2	912.1	806.5	501.4	486.3	573.4	227.6	54.2	12.3
1444-1042	0.0	145.3	674.9	1277.2	1177.6	1493.7	556.5	480.1	525.6	630.4	303.7	30.3	0.0
1444-1051	0.0	366.7	817.9	661.5	557.9	435.3	391.9	268.4	239.9	259.6	144.4	46.0	33.3
1444-1052	0.0	150.9	439.0	880.8	1056.2	755.1	457.2	301.1	233.3	306.3	0.0	23.9	24.1
1444-1057	0.0	429.4	1077.5	1026.3	686.3	733.3	416.1	338.6	297.9	277.5	178.8	53.6	18.3
N	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0.0	283.4	756.1	978.9	851.2	834.2	523.4	373.2	339.1	383.6	159.3	43.2	16.4
SD	0.0	115.5	210.2	215.6	233.3	358.3	151.4	95.7	131.8	171.0	104.7	13.0	11.6
SEM	0.0	47.1	85.8	88.0	95.2	146.3	61.8	39.1	53.8	69.8	42.8	5.3	4.7
Min	0.0	145.3	439.0	661.5	557.9	435.3	391.9	268.4	233.3	254.6	0.0	23.9	0.0
Median	0.0	304.1	762.3	960.6	814.5	744.2	484.6	344.2	274.6	291.9	161.6	48.6	15.3
Max	0.0	429.4	1077.5	1277.2	1177.6	1493.7	806.5	501.4	525.6	630.4	303.7	54.2	33.3
%CV	NA	41	28	22	27	43	29	26	39	45	66	30	71
GM	NA	261.2	730.1	958.3	824.5	778.1	507.7	363.4	319.9	355.9	NA	41.3	NA

NA: Not Applicable; ND: No Data; GM: Geometric Mean

[00347] Table 38. Individual and Mean Plasma Concentrations (ngEq/mL) of XL184-Half-Dimer using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	139.5	166.1	173.5	97.2	162.4	111.4	129.1	109.6	89.2	58.2	0.0	0.0
1444-1040	0.0	81.0	85.9	77.2	76.6	67.1	66.7	52.1	60.2	75.2	0.0	0.0	0.0
1444-1042	0.0	0.0	65.7	136.3	164.3	134.3	210.1	198.0	216.3	295.1	130.0	0.0	0.0
1444-1051	0.0	132.3	213.3	198.6	186.7	138.3	158.0	98.8	154.6	124.1	69.5	31.7	0.0
1444-1052	0.0	140.9	236.4	234.6	203.0	222.9	192.0	190.2	254.7	171.2	0.0	47.7	10.7
1444-1057	0.0	204.9	235.7	160.3	166.6	183.3	137.7	137.8	172.0	175.6	78.7	12.7	0.0
N	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0.0	116.4	167.2	163.4	149.1	151.4	146.0	134.3	161.2	155.1	56.1	15.4	1.8
SD	0.0	69.3	75.5	54.0	50.6	52.6	52.8	55.2	70.4	80.0	49.9	20.1	4.4
SEM	0.0	28.3	30.8	22.0	20.7	21.5	21.5	22.5	28.8	32.6	20.4	8.2	1.8
Min	0.0	0.0	65.7	77.2	76.6	67.1	66.7	52.1	60.2	75.2	0.0	0.0	0.0
Median	0.0	135.9	189.7	166.9	165.5	150.4	147.9	133.5	163.3	147.7	63.9	6.4	0.0
Max	0.0	204.9	236.4	234.6	203.0	222.9	210.1	198.0	254.7	295.1	130.0	47.7	10.7
%CV	NA	60	45	33	34	35	36	41	44	52	89	131	245
GM	NA	NA	149.4	154.6	140.6	142.2	136.7	122.9	146.0	139.5	NA	NA	NA

** Co-eluted with Demethyl XL184 glucuronide B; NA: Not Applicable; GM: Geometric Mean

[00348] **Table 39. Individual and Mean Plasma Concentrations (ngEq/mL) of XL184-N-Oxide using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	0.0	175.4	224.8	189.5	232.5	183.2	144.4	143.6	140.5	73.8	0.0	8.9
1444-1040	0.0	66.3	217.5	321.2	304.2	327.1	293.7	268.4	319.9	309.6	103.3	38.1	10.7
1444-1042	0.0	0.0	131.0	331.2	344.9	161.7	284.1	110.9	69.4	111.0	100.1	0.0	0.0
1444-1051	0.0	0.0	200.6	221.9	181.3	153.4	137.5	135.2	129.0	208.3	85.1	0.0	0.0
1444-1052	0.0	0.0	132.1	195.6	325.7	235.5	235.9	133.9	104.0	160.6	0.0	0.0	0.0
1444-1057	0.0	87.9	215.0	340.5	252.8	237.0	216.4	167.0	178.6	229.0	60.4	34.2	0.0
N	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0.0	25.7	178.6	272.5	266.4	224.5	225.1	160.0	157.4	193.2	70.5	12.1	3.3
SD	0.0	40.4	39.4	65.1	69.9	63.0	59.7	56.1	87.7	71.6	38.1	18.7	5.1
SEM	0.0	16.5	16.1	26.6	28.5	25.7	24.4	22.9	35.8	29.2	15.5	7.6	2.1
Min	0.0	0.0	131.0	195.6	181.3	153.4	137.5	110.9	69.4	111.0	0.0	0.0	0.0
Median	0.0	0.0	188.0	273.0	278.5	234.0	226.2	139.8	136.3	184.5	79.5	0.0	0.0
Max	0.0	87.9	217.5	340.5	344.9	327.1	293.7	268.4	319.9	309.6	103.3	38.1	10.7
%CV	NA	157	22	24	26	28	27	35	56	37	54	155	156
GM	NA	NA	174.7	265.9	258.3	217.3	218.0	153.3	140.3	182.5	NA	NA	NA

NA: Not Applicable; ND: No Data; GM: Geometric Mean

[00349] Table 40. Individual and Mean Plasma Concentrations (ngEq/mL) of XL184-Sulfate* using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	167.5	270.2	350.0	568.8	575.3	543.8	405.8	422.7	381.1	280.7	115.5	41.6
1444-1040	0.0	126.4	426.4	559.5	789.6	740.4	776.3	606.7	571.2	866.9	488.1	252.7	41.0
1444-1042	0.0	0.0	247.5	504.7	589.0	452.6	718.1	207.2	264.6	630.8	418.0	101.1	15.6
1444-1051	0.0	94.8	269.3	458.4	459.9	502.0	389.9	316.1	470.7	515.7	312.6	122.3	75.3
1444-1052	0.0	132.6	362.7	541.6	459.9	535.8	532.0	402.3	366.7	501.3	248.3	0.0	18.5
1444-1057	0.0	282.5	460.4	600.8	588.5	673.9	496.0	435.0	545.0	529.2	311.0	192.8	19.4
N	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0.0	134.0	339.4	502.5	576.0	580.0	576.0	395.5	440.2	570.8	343.1	130.7	35.2
SD	0.0	92.4	90.4	89.0	120.8	108.5	144.4	132.7	114.6	165.4	91.1	86.0	22.8
SEM	0.0	37.7	36.9	36.4	49.3	44.3	59.0	54.2	46.8	67.5	37.2	35.1	9.3
Min	0.0	0.0	247.5	350.0	459.9	452.6	389.9	207.2	264.6	381.1	248.3	0.0	15.6
Median	0.0	129.5	316.5	523.2	578.7	555.6	537.9	404.1	446.7	522.5	311.8	118.9	30.2
Max	0.0	282.5	460.4	600.8	789.6	740.4	776.3	606.7	571.2	866.9	488.1	252.7	75.3
%CV	NA	69	27	18	21	19	25	34	26	29	27	66	65
GM	NA	NA	329.6	495.2	566.1	571.8	561.0	375.9	426.4	552.7	333.8	NA	29.9

*** Co-eluted with Half-dimer methyl ester; NA: Not Applicable; ND: No Data; GM: Geometric Mean

[00350] Table 41. Individual and Mean Plasma Concentrations (ngEq/mL) of Demethyl Half-Dimer Sulfate using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	0.0	0.0	0.0	0.0	0.0	110.2	105.9	182.6	417.5	360.9	313.3	129.8
1444-1040	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	60.1	87.4	172.2	165.5	71.8
1444-1042	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	127.1	315.2	373.2	391.1	175.0
1444-1052	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	155.6	216.2	532.7	389.9	240.7
N	4	4	4	4	4	4	4	4	4	4	4	4	4
Mean	0.0	0.0	0.0	0.0	0.0	0.0	27.6	26.5	131.4	259.1	359.8	315.0	154.3
SD	0.0	0.0	0.0	0.0	0.0	0.0	55.1	53.0	52.6	140.9	147.5	106.1	71.4
SEM	0.0	0.0	0.0	0.0	0.0	0.0	27.6	26.5	26.3	70.5	73.8	53.0	35.7
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	60.1	87.4	172.2	165.5	71.8
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	141.4	265.7	367.1	351.6	152.4
Max	0.0	0.0	0.0	0.0	0.0	0.0	110.2	105.9	182.6	417.5	532.7	391.1	240.7
%CV	NA	NA	NA	NA	NA	NA	200	200	40	54	41	34	46
GM	NA	NA	NA	NA	NA	NA	NA	NA	121.4	223.3	333.4	298.2	140.8

GM: Geometric Mean; NA: Not Applicable

Subjects whose PK profile did not contain more than five consecutive data points with a quantifiable concentration value.

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1051	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	113.1	262.0	299.5	143.8
1444-1057	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	142.9	249.6	149.3	157.1

[00351] Table 42. Individual and Mean Plasma Concentrations (ngEq/mL) of P5 using a Radio-Quantitati Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1042	0.0	0.0	75.0	129.9	150.2	189.8	246.6	173.8	151.8	147.1	0.0	0.0	7.6
1444-1051	0.0	69.2	126.6	144.7	114.6	116.8	106.6	102.2	0.0	0.0	61.8	31.8	0.0
1444-1052	0.0	42.1	76.1	189.6	151.9	144.0	83.4	83.0	84.9	137.1	89.9	0.0	0.0
N	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	0.0	37.1	92.6	154.7	138.9	150.2	145.5	119.7	78.9	94.7	50.6	10.6	2.5
SD	0.0	34.9	29.5	31.1	21.1	36.9	88.3	47.9	76.1	82.2	46.0	18.4	4.4
SEM	0.0	20.1	17.0	17.9	12.2	21.3	51.0	27.6	43.9	47.5	26.6	10.6	2.5
Min	0.0	0.0	75.0	129.9	114.6	116.8	83.4	83.0	0.0	0.0	0.0	0.0	0.0
Median	0.0	42.1	76.1	144.7	150.2	144.0	106.6	102.2	84.9	137.1	61.8	0.0	0.0
Max	0.0	69.2	126.6	189.6	151.9	189.8	246.6	173.8	151.8	147.1	89.9	31.8	7.6
%CV	NA	94	32	20	15	25	61	40	96	87	91	173	173
GM	NA	NA	89.7	152.7	137.8	147.2	129.9	113.8	NA	NA	NA	NA	NA

GM: Geometric Mean; NA: Not Applicable

Subjects whose PK profile did not contain more than five consecutive data points with a quantifiable concentration value.

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	0.0	0.0	0.0	146.8	0.0	0.0	0.0	0.0	112.5	0.0	37.7	11.4
1444-1040	0.0	0.0	0.0	126.4	145.3	160.8	0.0	0.0	81.0	103.9	0.0	0.0	0.0
1444-1057	0.0	0.0	0.0	123.7	184.7	0.0	131.9	86.6	128.2	98.7	0.0	21.5	0.0

[00352] Table 43. Individual and Mean Plasma Concentrations (ngEq/mL) of P7 using a Radio-Quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1051	0.0	55.4	76.8	95.3	72.7	85.0	57.1	38.4	0.0	0.0	0.0	0.0	0.0
N	1	1	1	1	1	1	1	1	1	1	1	1	1
Mean	0.0	55.4	76.8	95.3	72.7	85.0	57.1	38.4	0.0	0.0	0.0	0.0	0.0
SD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SEM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Min	0.0	55.4	76.8	95.3	72.7	85.0	57.1	38.4	0.0	0.0	0.0	0.0	0.0
Median	0.0	55.4	76.8	95.3	72.7	85.0	57.1	38.4	0.0	0.0	0.0	0.0	0.0
Max	0.0	55.4	76.8	95.3	72.7	85.0	57.1	38.4	0.0	0.0	0.0	0.0	0.0
%CV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GM	NA	55.4	76.8	95.3	72.7	85.0	57.1	38.4	NA	NA	NA	NA	NA

GM: Geometric Mean; NA: Not Applicable

Subjects whose PK profile did not contain more than five consecutive data points with a quantifiable concentration value.

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1040	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1042	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1052	0.0	0.0	0.0	110.5	156.0	0.0	87.1	0.0	0.0	0.0	0.0	0.0	0.0
1444-1057	0.0	0.0	106.9	0.0	0.0	106.2	54.2	56.4	0.0	0.0	0.0	0.0	0.0

[00353] Table 44. Individual Plasma Concentrations (ngEq/mL) of P2 using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 μCi) to Healthy Male Subjects

Subjects whose PK profile did not contain more than five consecutive data points with a quantifiable concentration value.

	Time (hours)												
Subject	0	0.5	1	2	3	4	5	8	14	24	72	168	336
1444-1023	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	41.5	0.0	0.0	0.0
1444-1040	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1042	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1051	0.0	0.0	0.0	0.0	0.0	49.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1444-1052	0.0	0.0	58.7	0.0	74.1	0.0	0.0	72.7	0.0	0.0	0.0	0.0	0.0
1444-1057	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	46.3	0.0	0.0	0.0

[00354] Table 45. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of XL184 using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1023	895	1.98	29900	8890	17400	15.0	31100	0.00876	79.1
1444-1040	1130	2.00	52600	14300	33500	22.5	53700	0.0119	58.0
1444-1042	1490	4.00	53600	15200	37600	20.8	55000	0.0215	32.2
1444-1051	818	1.00	33200	7660	17400	25.1	38000	0.00685	101
1444-1052	1060	3.00	21300	8770	16100	10.2	24000	0.00909	76.2
1444-1057	1080	1.00	37700	9600	20600	26.4	39800	0.00906	76.5
N	6	6	6	6	6	6	6	6	6
Mean	1080	2.16	38100	10700	23800	20.0	40300	0.0112	70.5
SD	234	1.17	12800	3170	9340	6.24	12300	0.0053	23.2
SEM	95.5	0.48	5240	1300	3810	2.55	5010	0.00216	9.48
Min	818	1.00	21300	7660	16100	10.2	24000	0.00685	32.2
Median	1070	1.99	35500	9250	19000	21.7	38900	0.00908	76.4
Max	1490	4.00	53600	15200	37600	26.4	55000	0.0215	101
%CV	22	54	34	30	39	31	30	47	33
GM	1060	1.90	36200	10400	22400	19.0	38700	0.0104	66.6

GM: Geometric Mean; [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution.

[00355] Table 46. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of XL184-Half-dimer using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1023	174	1.98	6290	2750	6290	21.0	3.15	NR	NR	NR
1444-1040	85.9	1.00	1550	1550	3360	2.95	0.664	NR	NR	NR
1444-1042	295	24.03	15200	5000	15200	28.4	5.91	NE	NE	NE
1444-1051	213	1.00	12900	3370	8020	38.9	9.77	NR	NR	NR
1444-1052	255	14.00	16400	5050	9160	77.0	7.89	17600	0.00889	77.9
1444-1057	236	1.00	14400	3940	10000	38.2	10.1	15100	0.0184	37.8
N	6	6	6	6	6	6	6	2	2	2
Mean	210	7.17	11100	3610	8680	34.4	6.25	16400	0.0136	57.9
SD	73.0	9.72	5890	1350	3980	24.7	3.76	1770	0.00672	28.4
SEM	29.8	3.97	2400	552	1620	10.1	1.54	1250	0.00476	20.1
Min	85.9	1.00	1550	1550	3360	2.95	0.664	15100	0.00889	37.8
Median	225	1.49	13700	3650	8590	33.3	6.90	16400	0.0136	57.9
Max	295	24.03	16400	5050	15200	77.0	10.1	17600	0.0184	77.9
%CV	35	136	53	37	46	72	60	11	49	49
GM	196	2.96	8760	3360	7870	24.2	4.61	16300	0.0128	54.3

** Co-eluted with Demethyl XL184 glucuronide B; GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent);

[b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; NE: Not Estimable; NR: Not reportable since AUC_{0-t} / AUC_{0-inf} ratio < 0.80

[00356] Table 47. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of XL184-N-oxide using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1023	233	4.00	13100	3650	8790	43.8	6.55	14100	0.0086	80.6
1444-1040	327	4.00	27900	7050	17000	53.0	12.0	29100	0.00847	81.8
1444-1042	345	3.00	8180	3110	8180	15.3	3.18	NR	NR	NR
1444-1051	222	2.00	10700	3660	10700	32.2	8.10	NR	NR	NR
1444-1052	326	3.00	3580	3560	7430	16.8	1.72	NR	NR	NR
1444-1057	341	2.00	16300	4790	11700	43.2	11.4	19100	0.0122	56.9
N	6	6	6	6	6	6	6	3	3	3
Mean	299	3.00	13300	4300	10600	34.1	7.16	20800	0.00976	73.1
SD	56.0	0.89	8360	1460	3490	15.4	4.20	7640	0.00212	14.0
SEM	22.9	0.37	3410	594	1430	6.30	1.71	4410	0.00122	8.11
Min	222	2.00	3580	3110	7430	15.3	1.72	14100	0.00847	56.9
Median	327	3.00	11900	3650	9750	37.7	7.33	19100	0.0086	80.6
Max	345	4.00	27900	7050	17000	53.0	12.0	29100	0.0122	81.8
%CV	19	30	63	34	33	45	59	37	22	19
GM	294	2.88	11100	4140	10200	30.7	5.84	19900	0.00961	72.1

GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution; NR: Not reportable since AUC_{0-t} / AUC_{0-inf} ratio < 0.80

[00357] Table 48. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of XL184-Sulfate* using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects**

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1023	575	4.00	58100	9980	25900	194	29.1	63800	0.00722	96.0
1444-1040	867	24.03	108000	15700	48200	205	46.3	113000	0.00958	72.3
1444-1042	718	5.00	69300	9370	34500	129	26.9	70500	0.0121	57.2
1444-1051	516	24.08	67600	10200	30100	204	51.2	80000	0.00606	114
1444-1052	542	1.98	41700	10200	28200	196	20.1	43400	0.0103	67.1
1444-1057	674	4.00	74500	12300	32500	198	52.1	76400	0.0101	68.4
N	6	6	6	6	6	6	6	6	6	6
Mean	649	10.52	69900	11300	33200	188	37.6	74500	0.00923	79.2
SD	132	10.53	22000	2360	7940	29.1	13.9	22900	0.00221	21.4
SEM	54.0	4.30	8970	964	3240	11.9	5.67	9330	0.000901	8.73
Min	516	1.98	41700	9370	25900	129	20.1	43400	0.00606	57.2
Median	625	4.50	68500	10200	31300	197	37.7	73500	0.00984	70.4
Max	867	24.08	108000	15700	48200	205	52.1	113000	0.0121	114
%CV	20	100	31	21	24	15	37	31	24	27
GM	638	6.71	67100	11100	32500	185	35.3	71600	0.00899	77.0

*** Co-eluted with Half-dimer methyl ester; GM: Geometric Mean; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution;

[00358] Table 49. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of Demethyl Half-dimer Sulfate using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1023	418	24.00	92500	4250	22900	309	46.3	NR	NR	NR
1444-1040	172	72.00	43300	917	7150	82.3	18.6	NR	NR	NR
1444-1042	391	168.00	103000	2590	19100	192	40.0	NE	NE	NE
1444-1052	533	71.98	117000	2320	20300	549	56.3	NR	NR	NR
N	4	4	4	4	4	4	4	0	0	0
Mean	379	84.00	89000	2520	17400	283	40.3	NA	NA	NA
SD	151	60.40	32000	1370	7000	200	15.9	NA	NA	NA
SEM	75.4	30.20	16000	683	3500	100	7.97	NA	NA	NA
Min	172	24.00	43300	917	7150	82.3	18.6	NA	NA	NA
Median	405	71.99	97800	2460	19700	251	43.2	NA	NA	NA
Max	533	168.00	117000	4250	22900	549	56.3	NA	NA	NA
%CV	40	72	36	54	40	71	40	NA	NA	NA
GM	350	67.61	83400	2200	15900	228	37.3	NA	NA	NA

GM: Geometric Mean; NR: Not reportable since AUC_{0-t} / AUC_{0-inf} ratio < 0.80;
NE: Not Estimable; NA: Not Applicable; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution

[00359] Table 50. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of P5 using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1042	247	5.00	7920	3750	7280	14.8	3.08	8720	0.00945	73.4
1444-1051	145	2.00	7150	1180	2660	21.5	5.41	NR	NR	NR
1444-1052	190	1.98	7910	2470	7920	37.1	3.80	NR	NR	NR
N	3	3	3	3	3	3	3	1	1	1
Mean	194	2.99	7660	2470	5950	24.5	4.10	8720	0.00945	73.4
SD	51.1	1.74	442	1290	2870	11.4	1.19	NA	NA	NA
SEM	29.5	1.00	255	743	1660	6.61	0.689	NA	NA	NA
Min	145	1.98	7150	1180	2660	14.8	3.08	8720	0.00945	73.4
Median	190	2.00	7910	2470	7280	21.5	3.80	8720	0.00945	73.4
Max	247	5.00	7920	3750	7920	37.1	5.41	8720	0.00945	73.4
%CV	26	58	6	52	48	47	29	NA	NA	NA
GM	189	2.71	7650	2220	5350	22.8	3.99	8720	0.00945	73.4

GM: Geometric Mean; NR: Not reportable since AUC_{0-t} / AUC_{0-inf} ratio < 0.80; NA: Not Applicable; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites);

C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution

[00360] Table 51. Individual and Descriptive Statistics of Plasma Pharmacokinetic Parameters of P7 using a Radio-quantitative Method following a Single 175 mg Oral Administration of [^{14}C]-XL184 (100 µCi) to Healthy Male Subjects

Subject	C_{max} (ngEq/mL)	t_{max} (h)	AUC_{0-t} (h·ngEq/mL)	AUC_{0-24} (h·ngEq/mL)	AUC_{0-72} (h·ngEq/mL)	Ratio[a] (%)	Ratio[b] (%)	AUC_{0-inf} (h·ngEq/mL)	k_{el} (1/h)	$t_{½}$ (h)
1444-1051	95.3	2.00	510	625	625	1.54	0.386	NR	NR	NR
N	1	1	1	1	1	1	1	0	0	0
Mean	95.3	2.00	510	625	625	1.54	0.386	NA	NA	NA
SD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SEM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Min	95.3	2.00	510	625	625	1.54	0.386	NA	NA	NA
Median	95.3	2.00	510	625	625	1.54	0.386	NA	NA	NA
Max	95.3	2.00	510	625	625	1.54	0.386	NA	NA	NA
%CV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GM	95.3	2.00	510	625	625	1.54	0.386	NA	NA	NA

GM: Geometric Mean; NR: Not reportable since AUC_{0-t} / AUC_{0-inf} ratio < 0.80; NA: Not Applicable; [a]: ratio of AUC_{0-t} (metabolite)/ AUC_{0-t} (parent); [b]: ratio of AUC_{0-t} (each analyte)/ AUC_{0-t} (parent + 6 measured metabolites); C_{max}, maximum observed concentration; T_{max}, time of the maximum concentration; AUC_{0-t}, area under the concentration-time curve from time zero to the time of the last measurable concentration; AUC_{0-24}, area under the concentration-time curve from time zero to 24 hours post XL184 dose; AUC_{0-72}, area under the concentration-time curve from time zero to 72 hours post XL184 dose; AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; k_{el}, apparent terminal elimination rate constant; $t_{1/2}$, apparent terminal elimination half-life; CL/F, apparent total body clearance; V/F, apparent total volume of distribution

[00361] Procedure for Preparation of Vehicle for [^{14}C]-XL184 for Oral Solution: PEG-400/TPGS/Ethanol 85/10/5 w/w/w

Example for 600 g - Scale amounts proportionally for other volumes desired.

1. Heat about 600 g of PEG 400 in an oven set at 50°C.
2. Heat about 100 g of TPGS in an oven set at 50°C. Heat till TPGS has completely liquefied.
3. Weigh a 1000 mL glass bottle with cap and record the weight.
4. Tare the balance.
5. Weigh 510 g of warm PEG 400 from step 1 into the glass bottle from step 4.
6. Tare the balance.
7. Weigh 60 g of TPGS from step 2 into the bottle from step 6.
8. Mix the contents of the bottle from step 7 by swirling gently.
9. Place the bottle from step 8 in an oven set at 50°C for about 30 minutes, swirl the contents intermittently to ensure that the solution is homogenous.
10. Remove the bottle from step 9 from the oven and allow it to cool to RT.
11. Place the bottle on the balance and tare the balance.
12. Weigh 30 g of ethanol into the bottle from step 11, seal the bottle with the cap, and mix the contents gently till the solution is homogenous.
13. Label the bottle as follows:

"Vehicle for [^{14}C(U)]XL184 for Oral Solution"

"Store tightly capped at 25°C to 37°C"

Preparation date and time

Use date and time (use within 24 hours of preparation).

Note: The vehicle must be stored between 25°C and 37°C. The vehicle, when exposed to temperatures below 25°C for extended duration (4-6 hours), might become cloudy due to precipitation of TPGS. If this happens then the vehicle may be heated to 37 °C to dissolve any precipitate. Handling to the vehicle at ambient temperature during preparation of the formulation is permissible.

[00362] Procedure for Preparation of Oral Solution of [^{14}C]-XL184

[00363] 175 mg/subject (salt basis); 100 μCi/subject; concentration of drug in vehicle is about 8 mg/mL (salt basis)

1. Prepare 500 g of vehicle according to instructions; include cinnamon flavoring (0.1% v/v).
2. Dispense about 263 mL of vehicle into tared dose prep container (suggest 500 mL quantity).
3. Add 2100 mg of unlabeled XL184.
4. Add approx. 10 mg of labeled XL184.
5. Dissolve drug in vehicle, according to instructions.
6. Weigh total amount.
7. Withdraw two or three aliquots of about 1 g each and determine radioactivity per unit weight, by LSC and drug potency.
8. Dispense about 22 mL aliquots for each subject and obtain accurate weight for each aliquot.
9. Administer each aliquot to subject.

[00364] Dose dispensed to each subject will be accurately determined by multiplying weight of each aliquot in Step 8 with activity determined in Step 7.

[00365] REFERENCES

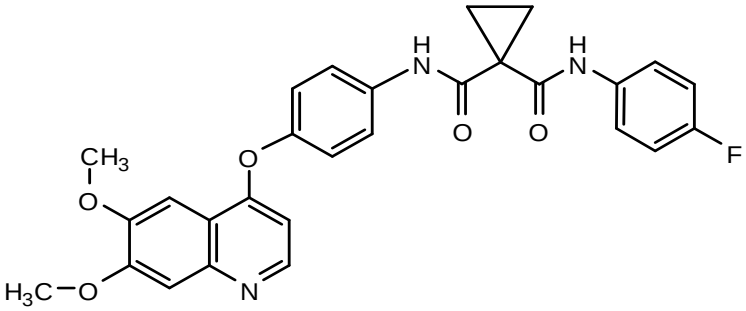
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[00367] Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011; 10(12):2298-308.

[00368] The foregoing disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

Claims

1. A liquid pharmaceutical composition comprising compound 1, or a pharmaceutically acceptable salt thereof.



Compound 1

and pharmaceutically acceptable carriers, wherein the carriers comprise ethanol, d-α-tocopheryl polyethylene glycol succinate (TPGS), and polyethyleneglycol.

2. The liquid pharmaceutical composition according to claim 1, wherein compound 1 is the L-malate salt (or S-malate salt).

3. The liquid pharmaceutical composition according to claim 1, wherein compound 1 is the D-malate salt (or R-malate salt).

4. The liquid pharmaceutical composition according to any one of claims 1-3, wherein the amount of compound 1, or a pharmaceutically acceptable salt thereof present in the liquid formulation, ranges from 1 mg to 200 mg.

5. The liquid pharmaceutical composition according to claim 4, wherein the amount of the compound of compound 1, or a pharmaceutically acceptable salt thereof present in the liquid formulation is 140 mg, or 120 mg, or 80 mg, or 60 mg, or 40 mg, or 20 mg.

6. The liquid pharmaceutical composition of claim 1, wherein the carriers comprise from 50% to 95% polyethyleneglycols (w/w), from 1% to 30% TPGS (w/w), and from 0.5% to 20% ethanol (w/w).

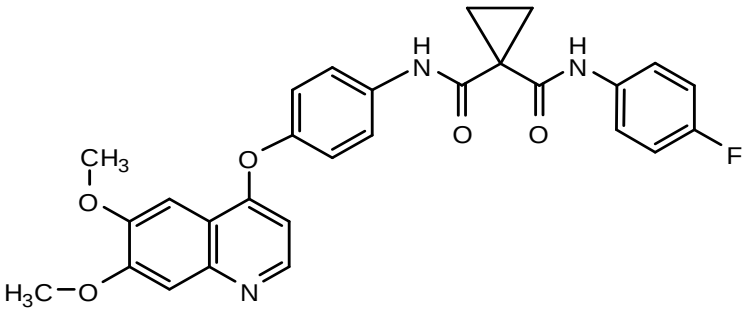
7. The liquid pharmaceutical composition of claim 1, as provided in any one of the following tables.

Ingredient	Theoretical Quantity (mg/unit dose)		
	20-mg Dose	40-mg Dose	60-mg Dose
Cabozantinib (S)-malate	25.34	50.68	76.02
Polyethylene glycol 400 (PEG 400)	2,934.88	5,869.77	8,804.65
d-α-tocopheryl polyethylene glycol succinate (TPGS)	345.28	690.56	1,035.84
Ethanol	172.64	345.28	517.92
Flavorings	3.45	6.91	10.36
Total	3,481.60	6,963.19	10,444.79

Ingredient	(% w/w)
Compound 1	0.73
Polyethylene glycol 400 (PEG 400)	84.30
d-α-tocopheryl polyethylene glycol succinate (TPGS)	9.92
Ethanol	4.96
Flavorings	0.10
Total	100

Ingredient	Theoretical Quantity (mg/unit dose)
Compound 1	175.00
Polyethylene glycol 400 (PEG 400)	20,268.53
d-α-tocopheryl polyethylene glycol succinate (TPGS)	2,384.53
Ethanol	1,192.27
Flavorings	23.85
Total	24,044.18

8. A liquid pharmaceutical composition for use in treating locally advanced or metastatic solid tumors, the liquid pharmaceutical composition comprising compound 1



Compound 1

or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable carriers, wherein the pharmaceutically acceptable carriers comprise ethanol, d-α-tocopheryl polyethylene glycol succinate (TPGS), and polyethyleneglycol.

9. The liquid pharmaceutical composition for use according to claim 8, wherein compound 1 is to be administered as the L-malate salt (or S-malate salt).

10. The liquid pharmaceutical composition for use according to claim 8, wherein compound 1 is to be administered as the D-malate salt (or R-malate salt).

11. The liquid pharmaceutical composition for use according to any one of claims 8-10, wherein the locally advanced or metastatic solid tumors is advanced urothelial carcinoma or renal cell carcinoma.

12. The liquid pharmaceutical composition for use according to claim 8, wherein compound 1, or a pharmaceutically acceptable salt thereof is to be administered in a liquid dosage form once daily with fasting in an amount of 140 mg, 120 mg, 100 mg, 95 mg, 90 mg, 85 mg, 80 mg, 75 mg, 70 mg, 65 mg, 60 mg, 55 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, or 5 mg.

13. The liquid pharmaceutical composition for use according to claim 12, wherein compound 1, or a pharmaceutically acceptable salt thereof is to be administered in the liquid pharmaceutical composition once daily with fasting in an amount of 140 mg, 120 mg, 80 mg, 60 mg, 40 mg, or 20 mg.

14. The liquid pharmaceutical composition for use according to claim 8, wherein the carriers comprise from 50% to 95% polyethyleneglycols (w/w), from 1% to 30% TPGS (w/w), and from 0.5% to 20% ethanol (w/w).

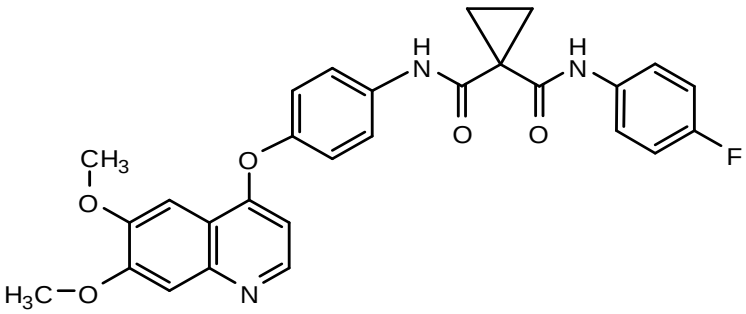
15. The liquid pharmaceutical composition for use according to claim 8, wherein the liquid pharmaceutical composition is as provided in any one of the following tables.

Ingredient	**Theoretical Quantity (mg/unit dose)**		
	20-mg Dose	**40-mg Dose**	**60-mg Dose**
Cabozantinib (S)-malate	25.34	50.68	76.02
Polyethylene glycol 400 (PEG 400)	2,934.88	5,869.77	8,804.65
d-α-tocopheryl polyethylene glycol succinate (TPGS)	345.28	690.56	1,035.84
Ethanol	172.64	345.28	517.92
Flavorings	3.45	6.91	10.36
Total	3,481.60	6,963.19	10,444.79

Ingredient	**(% w/w)**
Compound 1	0.73
Polyethylene glycol 400 (PEG 400)	84.30
d-α-tocopheryl polyethylene glycol succinate (TPGS)	9.92
Ethanol	4.96
Flavorings	0.10
Total	100

Ingredient	**Theoretical Quantity (mg/unit dose)**
Compound 1	175.00
Polyethylene glycol 400 (PEG 400)	20,268.53
d-α-tocopheryl polyethylene glycol succinate (TPGS)	2,384.53
Ethanol	1,192.27
Flavorings	23.85
Total	24,044.18

16. Use of compound 1



Compound 1

in the manufacture of a liquid pharmaceutical composition for treating locally advanced or metastatic solid tumors, wherein the liquid pharmaceutical composition comprises compound 1 or a pharmaceutically acceptable salt thereof, and pharmaceutically acceptable carriers, wherein the pharmaceutically acceptable carriers comprise ethanol, d-α-tocopheryl polyethylene glycol succinate (TPGS), and polyethyleneglycol.

17. The use according to claim 16, wherein compound 1 is to be administered as the L-malate salt.

18. The use according to claim 16, wherein compound 1 is to be administered as the D-malate salt.

19. The use according to claim 16, wherein the carriers comprise from 50% to 95% polyethyleneglycols (w/w), from 1% to 30% TPGS (w/w), and from 0.5% to 20% ethanol (w/w).

20. The use according to any one of claims 16-19, wherein the locally advanced or metastatic solid tumors is advanced urothelial carcinoma or renal cell carcinoma.